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THE CHICAGO MEDICAL SCHOOL

QUARTERLY

VOLUME 15, NUMBER 3 SUMMER 1954

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THE CHICAGO MEDICAL SCHOOL
QUARTERLY
VOLUME 15 JUNE 1954 NUMBER 3

SYMPOSIUM ON CARDIAC DISEASES:

I. CARDIAC FAILURE

Causes and Mechanism

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DEFINITIONS

Circulatory failure occurs when the blood flow of the capillaries is not adequate for the needs of the tissues. It may be *absolute*, when there is an actual inadequacy, or *relative*, when the inadequacy exists only because the needs are increased.

Circulatory failure may occur either because there is a reduction of the circulating blood, as in hemorrhage or shock, or because the capacity of the circulatory system is increased, as in peripheral vasodilation. In both cases, reduced venous return is responsible for the failure. However, circulatory failure may be of a different type if caused by heart failure.

Heart failure is *absolute* if the heart has actually reduced its work; it is *relative* if the heart maintains or even increases its work, but this is inadequate in the presence of increased requirements. Heart failure may be acute, subacute, or chronic.

Acute heart failure is due to a sudden primary or secondary disturbance of the heart; the resulting clinical picture resembles that of shock and is revealed by signs of arterial depletion.

Subacute or chronic heart failure, on the contrary, is mostly revealed by signs and symptoms of congestion of the venous side of the cardiovascular system.

The clinical picture of heart failure always occurs in persons with a weak heart. However, its appearance may be hastened and its existence revealed at an earlier stage, by severe vascular or valvular lesions.

CAUSES

Heart failure may occur as the result of any lesion of the heart and of any diffuse lesion of the vessels. The following classification permits a better understanding of its mechanism.

(a) *Diseases causing strain of the left ventricle, frequently also of the large arteries and the coronaries.* These include arterial hypertension, atherosclerosis of the aorta and aortitis, aortic insufficiency or stenosis, coarctation of the aorta, patent ductus arteriosus, and some cases of constrictive pericarditis. In all these conditions, the left ventricle is hypertrophied.

(b) *Diseases causing strain of the right ventricle, and frequently also of the pulmonary artery and the vessels of the lesser circulation.* These include mitral stenosis, acute or chronic cor pulmonale, patent foramen ovale, and pulmonary stenosis. In all these diseases, the right

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ventricle is hypertrophied; in mitral stenosis, the left atrium participates in the strain.

(c) *Diseases where the strain is felt by both sections of the heart.* Among these are combined valvular defects, ventricular septal defect, certain atypical cases of patent ductus arteriosus, arteriovenous fistulae, thyroid heart disease, disturbances of the rate and rhythm, diffuse myocardial fibrosis, coronary heart disease, beri-beri heart disease, and many cases of constrictive pericarditis.

Whatever the underlying cardiovascular disease, various factors may precipitate congestive failure. Among them, strenuous physical exertion, emotion, exposure to cold, and overabundance of food and drink, are common. Others are: coronary occlusion; acute infection; rheumatic carditis; pulmonary embolism; surgical intervention; acute gall bladder colic; pregnancy; and other less frequent conditions.

Chronic vitamin and protein deficiencies and several poisons favor cardiac failure. Excessive dosage or extremely prolonged action of digitalis may damage the myocardium, thereby favoring failure. However, the extent and importance of this digitalis effect is controversial.

MECHANISM OF HEART FAILURE

The circulatory apparatus is a closed system with many safety devices. The continuous motion of the blood is due to the action of four separate pumps. As the atria have a weak action and act mainly as reservoirs, two pumps actually maintain the circulation, the right and left ventricles.

A dam placed in the course of a river raises the level of the stream above the obstacle and lowers the level below; in the same way an obstacle placed in the course of a closed circuit (valvular stenosis, coarctation) raises the pressure above and decreases the pressure in the section below[5]. In such cases, the increased pressure (or the large caliber) in the chamber or vessel above the obstacle is not due to heart failure. Thus, distention of the left atrium and pulmonary vessels in mitral stenosis, or of the right atrium, venous system, and liver in tricuspid stenosis, is due to redistribution of the blood and does not imply heart failure. Again, the action of the obstacle on the section below is such that decreased pressure or lower output may be the result of valvular stenosis or vascular narrowing without implying that the heart is weak.

Another simple scheme of circulation includes the action of a pump and shows that when a weak action of the pump follows a stronger action, a rise of "venous pressure" takes place[18,19].

Cardiac Reserve

Cardiac reserve is a clinical term which is applied to the difference between the actual work of the heart and the maximum work which it is able to perform[1]. Cardiac reserve is reduced by: (a) *increase of cardiac work* (ventricular strain)—the figure of actual work is higher and nearer to the maximum possible work; (b) *decrease of efficiency* (latent ventricular failure)—the figure of maximum possible work is lower and nearer to the actual work; (c) *both.*

Cardiac reserve is reduced when valvular defects, vascular lesions, or inefficient cardiac action require permanently increased cardiac work in the presence of latent failure.

The decreased contractility of the heart may cause effects in two systems:

(a) *In the arterial system;* this is revealed by reduced flow, reduced pressure, or both, and has been called *forward failure.* It corresponds to a state of arterial depletion[20].

(b) *In the pulmonary circulation and the venous system;* this is revealed by increased venous pressure and distention of the veins and liver and has been called *backward failure.* It corresponds to a state of venous congestion[20].

As already stated, these arterial and venous phenomena may be simulated by the results of valvular or vascular lesions without actual failure.

The Concept of Reserve Power

The same differential concept which is implied in the definition of cardiac

reserve may be applied to other cardiovascular phenomena. Any cardiac lesion which causes congestion of the lungs reduces the "reserve power" of the lungs for accomodating a greater amount of blood when heart failure occurs. Any cardiac lesion which causes congestion of the liver reduces the "reserve power" of the liver for accomodating a greater amount of blood when heart failure occurs. Any decreased output, due to aortic stenosis, reduces the "reserve power" of the aorta and the arterial system whenever the heart reduces its output. Therefore, any change in the distribution of the blood, in the pressure of one of the vascular systems, and in the volume of a cardiac chamber, artery, or vein, existing before heart failure sets in, inevitably causes severe results in that section, system, or organ, because of reduced "reserve power," when heart failure occurs. For this reason, a basically similar process of cardiac failure may cause diverse clinical pictures in patients with different lesions of the heart and vessels.

The observation that damage to the right heart may not be followed by increased venous congestion [6] led to admission that a long and complex chain of events connects heart failure with increased venous pressure. Without changing the main concept that cardiac failure is the primary and basic disturbance, this resulted in a better evaluation of several important phenomena, including high venous tonus [22] and renal retention of water and sodium[23].

It is now admitted that the increase of blood volume is an important factor, on the one hand in causing signs of congestion and, on the other, in increasing the severity of cardiac failure. A vicious circle is created by the fact that increased blood volume is due to water and sodium retention because of renal dysfunction, while this renal dysfunction is an indirect result of cardiac failure.

Sodium Retention

The retention of sodium is caused by either: (a) low filtration rate secondary to decreased renal blood flow with a normal (or even subnormal) tubular absorption[24]; or (b) normal filtration rate with increased tubular absorption[25].

Low filtration rate seems to be related to initially low cardiac output plus compensatory vasoconstriction of the renal arterioles. High venous renal pressure, related to the complex causes of venous hypertension in general, may increase renal dysfunction.

The renal dysfunction, however, has even a more complex mechanism because sodium and water retention seem to be partly independent and caused by special endocrine disorders. Excessive retention of water followed by retention of salt is found in many conditions suggesting an excessive amount of posterior pituitary hormone. On the other hand, excessive retention of salt followed by retention of water is found in other cases suggesting an excessive amount of adrenal cortical hormone[26]. The problem is further complicated by the interrelation between the two hormones. Moreover, an excess of adrenocorticotrophic hormone might be the cause of excessive corticoadrenal secretion. These disturbances may be due to the effect of anoxia on either the anterior or the posterior pituitary or to insufficient destruction of either hormone by the congested liver[27].

TYPES OF HEART FAILURE

Studies dealing with velocity of circulation or cardiac output have revealed two different types of cardiac failure.

The first type is encountered chiefly in rheumatic, hypertensive, and coronary heart diseases. It is characterized by *increased circulation time and reduced cardiac output*[20,22]. The second is found in anemic, thyroid, and beriberi heart diseases, in certain cases of chronic cor pulmonale, in patent ductus arteriosus, in arteriovenous fistulae, and in some cases of Paget's disease. In such cases *decreased circulation time and normal or increased cardiac output* occur. It is apparent that rheumatic valvular disease, cardiovascular lues, or hypertensive heart disease may also be associated with anemia, vitamin-B deficiency,

or hyperthyroidism causing, therefore, a *mixed type of cardiac failure with slightly increased or slightly decreased output and circulation time.* It should be emphasized that low-output failure is associated with an absolute decrease of cardiac reserve and, therefore, is an *absolute cardiac failure.* On the other hand, high-output failure is usually associated with a relative decrease of cardiac reserve because of increased requirements of the tissues, and therefore represents *relative cardiac failure.*

Isolated Ventricular Failure

The fact that the heart is composed of two main pumps, the right and left ventricles, working under different conditions, led to a brilliant and daring conception[2]: that each of them might become insufficient without the other being affected. This theory tried to explain different clinical pictures as the result of isolated failure of one or the other ventricle. *Right ventricular failure* would be revealed by exertional dyspnea, right ventricular enlargement, hepatic enlargement, and peripheral edema. *Left ventricular failure* would be revealed by anginal pain, paroxysmal dyspnea, and acute pulmonary edema[2]. A confirmation of this theory was found in the frequent occurrence of the former syndrome in patients with right ventricular strain (mitral stenosis) and of the latter in patients with left ventricular strain (aortic insufficiency, arterial hypertension). A reaction against excessive generalization of this theory was started by the author in 1932[3].

Experimental[4,6,19] and clinical[10] evidence seemed to confirm his views. Later studies by means of catheterization of the right heart[30,31] revealed a high diastolic pressure of the right ventricle in cases with right ventricular failure and a high systolic pressure of the right ventricle (with normal diastolic) in cases with left ventricular failure. Thus, clinical evidence of isolated ventricular failure was obtained. Moreover, it was proved that experimental compression of a coronary artery is followed by increased diastolic pressure of the left ventricle while right ventricular pressures and the filling pressure of the right atrium are still normal[32].

This reveals the possibility of isolated acute ventricular failure following diffuse coronary insufficiency. On the other hand, *chronic failure of one ventricle is usually followed by failure of the other on account of the multiple anatomical and functional connections between the two chambers.*

Whenever long standing mechanical obstacles or structural changes have occurred, striking differences between the pressures or capacities of the two chambers or two vascular districts may occur. When failure affects one ventricle predominantly or exclusively, the clinical manifestations appear first in that vascular district which is behind the weak chamber, even if the equilibrium is reestablished by subsequent weakening of the other chamber[1].

There is no doubt that certain signs due to heart failure frequently resemble signs caused by some valvular or vascular lesion. As previously stated, these signs are connected with a preexisting reduction of the "reserve power" of the affected organs. Therefore, any further increase of the sign is detected more easily because the clinical threshold of observation is quickly reached.

Enlargement of the liver occurs as a result of dynamic changes due to tricuspid stenosis. If the heart is weak, a slight, further increase of venous pressure is revealed immediately by palpation of an enlarged liver and by hepatic dysfunction.

Cerebral ischemia often occurs in aortic insufficiency. Weakening of the heart causes a decrease of cardiac output, and this is revealed by signs of cerebral anemia because the cerebral circulation is already near the threshold of clinical disturbance.

Pulmonary congestion is frequent in arterial hypertension and may cause exertional dyspnea. Any weakening of the heart causes severe dyspnea because the power of dilation of the pulmonary vessels is reduced.

Blood flow through the arteries of the legs is often reduced in cases with co-

arctation of the aorta or arteriosclerosis obliterans. The earliest sign of heart failure in such patients is intermittent claudication. Here the reduced cardiac output lowers the blood flow in the extremities below the level which permits exertion.

In conclusion, congestion and depletion may be caused by the hemodynamic effects of the cardiac disease, by cardiac failure, or both.

Starling's Law

The application of Starling's law to the hearts of sick patients was resisted by clinicians. It was stated that "while dilatation of a normal heart means greater power of contraction, dilatation of a sick heart means lesser power of contractions[7]." The contradiction between accepted clinical knowledge and physiological laws can be explained as follows: when the heart of a cardiac patient fails, its efficiency is reduced; an increase of work is obtained through dilatation; therefore, even if this dilatation is compensatory, it implies that the heart is weak. Moreover, excessive dilatation fails to increase the power of contraction.

The three mechanisms of adaptation of the heart are: increase of rate, increase of volume, and hypertrophy. Each has a critical limit above which the heart decreases its efficiency instead of increasing it. For the heart rate, the limit seems to be around two hundred, because higher rates do not permit a good diastolic filling. Dilatation ceases to be useful when the elastic limit of the fibers is exceeded and diastolic pressure begins to rise. Hypertrophy is not profitable if too severe, because the capillary network becomes insufficient in relation to the blood supply necessary for muscle metabolism. Then a vicious cycle takes place. The dilated and rapid heart contracts faster and faster, less and less effectively. The fact that an extremely dilated heart may be a mechanical obstacle to cardiorespiratory dynamics should also be taken into account.

Chronic Congestive Failure

Chronic congestive failure is the result of impairment of the contractility of the myocardium, even if vascular, renal, hepatic, nervous, and endocrine elements contribute to the development of the picture.

Cardiac failure may manifest itself either by decrease of cardiac work without venous engorgement (predominant picture of depletion), or by venous engorgement without decreased work (predominant picture of congestion). Only the ratio between work and venous conditions is a sure evidence of failure, because a normal heart may have decreased output, associated with decreased venous return, or venous engorgement, associated with increased output. In the first case, there is reduced cardiac volume; in the second, increased cardiac volume.

Venous pressure is not an adequate element for evaluating cardiac conditions because the flow may increase without a rise in pressure and *vice versa*, because of changing conditions of the venous wall.

Two different mechanisms have been discussed as possible causes for heart failure. The first consists of a decreased ability to release energy with a decreased oxygen consumption for a given diastolic size[8]. The second consists of a smaller conversion of the energy into useful work, *i.e.*, an impairment in the mechanical efficiency[9]. The second mechanism seems the most likely.

It should be kept in mind that different types of myocardial disturbances may occur. As already stated, increased requirements may cause a relative cardiac failure. In such cases, the metabolism and the contractile power of the cardiac fiber may be preserved, and the term *hemodynamic cardiac failure* should be used[28]. On the contrary, in most cases with absolute cardiac failure, a primary deficiency of contractility takes place following severe changes of the metabolism of the cardiac muscle. This is revealed by prolongation of electrical systole (Q-T interval of the electrocardiogram) and abbreviation of mechanical systole (distance from the first to the second sound of the phonocardiogram). For these cases, the name of *energetic-dynamic insufficiency* has been suggested[28].

SUMMARY

(1) Circulatory failure should be differentiated from heart failure.

(2) Heart failure may be absolute or relative. The latter may occur with normal cardiac output.

(3) The clinical picture of heart failure is revealed by signs of venous congestion and arterial depletion.

(4) Any cause of strain of the right or the left ventricle, or both, may be the cause of heart failure.

(5) Heart failure is preceded by a period of decreased "cardiac reserve." The decrease may be due to either increase of work (ventricular strain) or decrease of efficiency (latent failure).

(6) The complex picture of congestive failure includes several extracardiac elements. Among them are high venous tonus, increase of blood volume, and sodium retention. Endocrine elements (posterior pituitary and corticoadrenal) may be involved in the renal dysfunction which causes retention of sodium and water.

(7) Low output failure is a common type. Less common is high output failure, which is found in anemic, thyroid, and vitamin-B deficient hearts, as well as in arteriovenous fistulae and certain cases of chronic cor pulmonale.

(8) Right or left ventricular failure should be differentiated. However, total failure is the most common type.

(9) Ventricular failure is revealed by increased residual blood and higher diastolic pressure. Actual proof is given by right heart catheterization in cases with right ventricular failure.

(10) The three mechanisms of adaptation of the heart are increase of rate, increase of volume, and hypertrophy. Each has a critical limit above which the efficiency decreases. For this reason, there is a limit to the possibility of ventricular strain.

(11) Even if several extracardiac elements contribute to the picture of failure, it is the result of impaired contractility of the myocardium due to impaired mechanical efficiency.

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SYMPOSIUM ON CARDIAC DISEASES:

II. CARDIAC FAILURE

Diagnosis*

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There is no symptom or sign which is typical of cardiac failure. Any of these may be caused by dysfunction or disease of organs other than the heart. Therefore, the diagnosis of congestive heart failure can be made only by observation of several symptoms or signs and after an evaluation of all clinical and laboratory data.

As is often the case in medicine, congestive failure may be obvious and easy to diagnose in certain cases, while in others, recognition of the cause of the congestive picture may be difficult. This is because there are symptoms and signs which may simulate heart failure (dyspnea in obstructive emphysema, large liver of constrictive pericarditis). While the complaints may be minimal in the presence of definite failure, in other cases, the clinical picture is out of proportion to the physiological disturbance because of a cardiac neurosis.

EVALUATION OF SYMPTOMS AND SIGNS

History and physical examination of the patient are both important for diagnosis. Negative findings may be as useful as positive data.

Respiratory distress is the first and most prominent symptom of left heart failure. It appears in different forms. In general, *cardiac dyspnea* is a labored type of breathing with an increase of the respiratory rate. Dyspnea can be related to many factors. Physiological causes may be lack of physical training, obesity, or pregnancy. Pathological causes include many diseases which may interfere with respiration, *i.e.*, laryngeal, bronchial, pulmonary, pleural, or mediastinal diseases, metabolic disturbances (acidosis), anemia, and diseases of the nervous system (meningitis, encephalitis). In the early stages of mitral stenosis, dyspnea is due to congestion of the lungs caused by valvular obstruction and not to failure of the left ventricle.

The general picture, and the presence of symptoms and signs peculiar to each disease usually permits differentiation. Whenever evaluation of the cause of dyspnea is impossible, determination of the circulation time may supply important data.

Exertion

Exertion is the most common cause of dyspnea. Since even normal people are "short of breath" after exertion, the patient should be asked how many blocks he has to walk, or how many flights of stairs he has to climb before the onset of labored breathing. Moreover, it is important to ascertain how long the dyspnea lasts after the termination of exertion. The answer permits one to grade the severity of the dyspnea and, thus, the degree of cardiac failure.

In neurocirculatory asthenia, dyspnea is unrelated, or out of proportion to physical exertion, and is really a *sighing type* of respiration. In middle-aged, obese persons, cardiac dyspnea should be differentiated from the result of lack of physical training; the patient should be questioned about his average exertion and conditioning and whether he recently changed his habits.

Orthopnea is characterized by the fact that the patient feels better in the sitting than in the recumbent position. The patient should be asked how many pillows he uses at night and whether their number recently was increased.

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Paroxysmal Nocturnal Dyspnea

Paroxysmal nocturnal dyspnea. This name is given to acute attacks which are usually associated with left ventricular strain or failure. The patient, after having rested for a few hours, wakes suddenly, must sit up, and is severely dyspneic. The time of appearance of paroxysmal dyspnea may be used to differentiate dyspnea of a cardiac patient, which occurs mostly during the night, from that due to emphysema, which appears in the morning when the patient starts his physical activity. *Cardiac asthma* is a respiratory distress characterized by bronchoconstriction, wheezing, and rhonchi. Differentiation of cardiac asthma from bronchial asthma is important, because of their differing therapies. A history revealing repeated asthmatic attacks originating during childhood and a familial history of allergy or bronchitis suggests a bronchial origin. Evidence of heart disease (high blood pressure, valvular defects, angina pectoris) usually indicates, on the contrary, that dyspnea is related to heart failure. It should be kept in mind, however, that both types of dyspnea may occur together, especially in chronic cor pulmonale. Whenever the data are insufficient for a correct diagnosis, circulation time tests may be of help. If these reveal increased values, the patient has cardiac asthma; if they are normal, there is usually bronchial asthma. If the severe condition of the patient prevents an accurate examination, *aminophylline* should be administered, because this drug is useful in both conditions. Later on, a definitive diagnosis may be made.

Acute pulmonary edema is a typical condition which occurs either after effort or during the night. It is similar to paroxysmal nocturnal dyspnea except for the presence of abundant foamy sputum and diffuse moist rales throughout the chest.

Cough

Cough. Cough may be an important symptom in cardiac failure. It should be differentiated from that due to broncholaryngeal, pulmonary, or pleural diseases. The last is usually accompanied by typical pleuritic pain, a friction rub, or both. In the first two conditions, cough is productive much more often than in cardiac failure. Cough is often present in paroxysmal nocturnal dyspnea and acute pulmonary edema. At times, early failure may be revealed by cough, and this is provoked by exertion or recumbency. In cardiac failure, cough can be due to reflexes, pulmonary congestion, pulmonary infarction, or bronchopneumonia. Therefore, it is a symptom which requires serious consideration.

Hemoptysis. Hemoptysis may be associated with acute pulmonary edema, but it is more characteristic of the pulmonary congestion of mitral stenosis and certain congenital shunts, *i.e.,* patent ductus arteriosus, atrial septal defects, and the Eisenmenger complex. It may also be due to pulmonary infarction.

Weakness and insomnia are also symptoms of cardiac failure, but they are such common phenomena that they cannot be used for diagnosis unless they are associated with other symptoms and signs. Weakness can be a prominent symptom in advanced failure and may be associated with anemia and loss of weight.

Hepatomegaly

When enlargement of the liver is present the patient complains of pain and a sensation of weight in the right upper quadrant. Other manifestations, such as anorexia, constipation, pyrosis, and eructation are secondary to congestion of the mucosa of the gastrointestinal tract.

Two manifestations of renal dysfunction seen in cardiac failure are *oliguria* and *nocturia.* Nocturnal frequency is typical of heart failure *only* if scanty urine is passed during the day. A careful comparison between fluid intake and output is also important for diagnosis.

Physical examination should start as soon as the patient meets the doctor. The way the patient walks, talks, undresses himself, sits, or lies down, should all be noted, for they often provide valuable information.

Physical examination should be complete, even if rapid. Fundoscopic exam-

ination and palpation of the femoral arteries are among the details which, if overlooked, may cause lack of essential data.

The weight of the patient is extremely important since an increase is suggestive of retention of water due to heart failure.

Cyanosis

Cyanosis may be observed in the lips, ear lobes, cheeks, fingers and toes, and oral mucosa. It may be more evident in the lying position, when engorgement of the systemic veins takes place. This important sign is due to slower blood flow in the periphery (*peripheral cyanosis*) and to congestion of the lungs because of heart failure. A different type of cyanosis is caused by incomplete oxygen saturation in the lungs (*central cyanosis*) and is typical of chronic cor pulmonale and complex malformations of the heart. Cyanosis may be favored by cardiac lesions in the absence of failure (mitral insufficiency and stenosis, constrictive pericarditis).

Palpation of the pulse and measurement of the pulse rate are important. Tachycardia, arrhythmia, and pulsus alternans are important signs. Tachycardia is increased by exercise and persists longer than in normal subjects. All other causes which increase the heart rate, such as fever, hyperthyroidism, and anemia, must be excluded. Arrhythmias may be due to premature contractions or atrial fibrillation. Pulsus alternans can be detected either by palpation of the radial artery or by measurement of the blood pressure.

In examining the lungs, one can detect the presence of subcrepitant rales at the bases (especially of the right lung), which are evidence of left heart failure. Differentiation of rales due to atelectasis from fine pleural rubs is important and is usually easy. In acute pulmonary edema, diffuse moist rales of various caliber are present. A pleural effusion may be due to heart failure, because of increased pressure of the azygos vein; it is more common on the right.

Examination of the Heart

Enlargement of the heart is almost always present in cardiac failure. It can be detected by percussion but inspection and palpation reveal that the apex beat is outside the normal limits. An x-ray confirms the enlargement. However, it should be kept in mind that it is often impossible to differentiate dilatation from hypertrophy, and both of these, from pericardial effusion. Therefore, enlargement of the cardiac dullness or of the cardiac silhouette may not be evidence of heart failure. On the other hand, if marked and rapid changes of heart size take place in repeated examinations, heart failure is likely. An obtuse cardiohepatic angle (revealed by percussion) may be due to either enlargement of the right atrium or pericardial effusion.

Several auscultatory data may be evidence of heart failure. A triple rhythm (gallop rhythm) is evidence of ventricular strain. It is heard best at the apex or over the xiphoid. In the first location, it is related to the left ventricle; in the second, to the right. The second pulmonic sound is often accentuated. A soft systolic murmur due to relative mitral or tricuspid insufficiency may be present. Sometimes a soft, early diastolic murmur, due to relative pulmonic insufficiency, can be heard over the pulmonic area. A diastolic rumble may be detected at the apex even without mitral lesions (relative mitral stenosis[1], *i.e.*, disproportion between the normal mitral orifice and a large left ventricle).

Examination of the Abdomen

Examination of the abdomen is important. In some cases, one of the first signs of right heart failure is enlargement of the liver. The liver is tender, soft, and regular, unless congestive failure has persisted for a long time. Venous pressure measurements and circulation time tests (see below) can be used in order to differentiate hepatic enlargement caused by heart failure from that due to hepatic diseases. The latter conditions are characterized by normal data.

Ascites may be present in heart failure. Ascitic fluid has the physical char-

acteristics of a transudate (low specific gravity), low protein content, negative Rivalta).

Heart failure frequently causes an increase of venous pressure. This can be grossly evaluated by examination of the peripheral veins at different levels. If venous engorgement is present only in part of the body, local causes, not heart failure, are likely.

Peripheral edema is another important and frequent indication of failure. It appears chiefly in the dependent parts of the body, hence the term *gravitational edema, i.e.*, the ankles if the patient has been standing; the sacrum and perineum if the patient has been lying down.

In general, cardiac edema is symmetrical, but it may be of varying severity in either leg. It is favored by varicose veins. Venous thrombosis, external pressure, and obstructive phenomena (tricuspid stenosis, constrictive pericarditis) may simulate the picture of cardiac edema, and must always be differentiated.

The diffuse edema of other diseases should be kept in mind and excluded. Among them, glomerulonephritis, toxic states, angioneurotic edema, vitamin-B1 deficiency, starvation, thyroid deficiency, and corticoadrenal excess, should be considered.

Heart failure in children with rheumatic carditis must be correctly diagnosed. The early signs of myocardial insufficiency appear in the following order[2]: enlarged liver, puffiness of the face, unexpected gain of weight, deviation of the electrical axis towards the right, diastolic gallop, and elevated venous pressure. These findings are probably due to the fact that the right ventricle is weaker and fails before the left.

Cor Pulmonale

In *acute* cor pulmonale, failure of the right ventricle is chiefly indicated by engorgement of the cervical veins and enlargement of the liver. In *chronic* cor pulmonale, dyspnea, cough, weakness, cyanosis, polycythemia, and low vital capacity, are due to the underlying pulmonary disease[3], and are aggravated by heart failure. When the right ventricle is enlarged and congestion of the systemic venous circulation is present, actual heart failure occurs. A large liver, gallop rhythm, severe cyanosis, and episodes of somnolence or dizziness due to cerebral anoxia, are typical of this syndrome. The episode of failure may occur suddenly and may be irreversible.

CIRCULATION FUNCTION TESTS

If, in spite of the careful collection of data, the diagnosis of heart failure is still in doubt, or a more exact evaluation of the severity of myocardial insufficiency is needed, functional tests may be of help.

The most useful tests are those which measure *circulation time*[4]. The term "circulation time" means the time required by a certain substance to progress from the point of entry into the body to an organ where subjective sensation or objective data reveal its arrival. Several extraneous factors influence circulation time, but the procedure is useful if the technique is adequate. Exercise shortens circulation time; therefore, the patient should be in a "basal condition" when the test is performed. High-output failure is frequently associated with shorter circulation time because the underlying conditions (anemia, fever, pregnancy, arteriovenous fistulae, thyrotoxicosis, severe anoxia, severe acidosis, and thiamine deficiency) cause rapid circulation. Cardiac failure in such cases may prolong circulation time to about normal or even figures above normal.

Technique

Technique. The patient should lie down for at least twenty minutes, try to relax, and should be instructed regarding the exact sensations which will be experienced. The arm must be at the level of the right atrium. After having entered the vein and released the tourniquet, the observer should wait about thirty seconds. The injection is then made in about one second. Many substances have been used for measuring circulation time: histamine, saccharine, amyl nitrite, calcium gluconate, fluorescein, brilliant vital red, carbon dioxide,

ether, sodium dehydrocholate, *etc.* They can be divided into two groups: those which measure the time of flow from a systemic vein (arm) to a peripheral artery and those which measure the time from a systemic vein (arm) to the lungs.

Fluorescein is particularly useful in infants because of its objective detection upon arrival at the fundus.

Decholin. 5 ml. of a 20% solution of sodium dehydrocholate are used. The patient feels a bitter taste in his mouth at the end point of the test. Normal values: 10-16 seconds (arm-to-tongue time).

Ether. 0.33 ml. of ether added to 0.5 ml. of physiologic saline solution is used. The patient starts to cough when he feels the ether which is eliminated through the alveoli and bronchi. Normal values: 6-10 seconds (arm-to-lung time).

In right heart failure, both ether and Decholin give a prolonged time. In left heart failure, only Decholin shows a prolongation.

Venous Pressure

Venous pressure. Measurement of venous pressure is important because it reveals the degree of congestion of the systemic veins. Venous pressure can be clinically evaluated in two ways:

(a) when the patient is sitting in bed in a semi-recumbent position, the jugular veins appear more or less engorged according to the increase of pressure in the superior vena cava and right atrium;

(b) when the patient is standing or sitting and keeps his arms down, the superficial veins are usually congested. When one arm is raised to the level of the shoulder, congestion normally disappears; if, on the contrary, congestion persists, this indicates that the venous pressure is increased. Should congestion persist even when the arm is raised above the level of the head, then venous pressure is severely increased.

More accurate values can be obtained by direct clinical determination. A simple apparatus can be used, *e.g.,* either an aneroid phlebomanometer calibrated in mm. of water (it should be checked from time to time against a direct water manometer) or an L-shaped calibrated glass tube[5]. The horizontal section of this tube is connected through rubber tubing with an 18 gauge needle; the tube is filled with sodium citrate solution in order to prevent clotting. The patient must lie down at least fifteen minutes before measurements. His right arm must be abducted at an angle of sixty degrees and be at the level of the right atrium (six to eight centimeters below the anterior surface of the chest). Values between nine and fifteen centimeters of water are normal. It should be kept in mind that increased venous pressure is usually evidence of heart failure. However, tricuspid defects, constrictive pericarditis, and mediastinal obstructions may also cause this phenomenon without heart failure. In several of these cases, the changes in pressure may vary from vein to vein.

Vital Capacity

Vital capacity. Heart failure results in a diminution of vital capacity, which decreases in proportion to congestion of the lungs. However, pulmonary diseases as well as a high level of the diaphragm (hepatomegaly due to right heart failure or hepatitis) cause the same phenomenon. Therefore, this test can be used only if correlated with other findings. Initial heart failure is usually revealed by changes of body weight, heart rate, and vital capacity. As the first two increase, the latter decreases[6].

Exertion tests. Functional tests have been devised for evaluation of the work of the heart. They are based on the ability of the patient to perform a certain amount of exercise and on the observation of the resulting changes of pulse, blood pressure, and respiration. So many factors and so many subjective elements complicate the results, that these are frequently difficult to evaluate or are even unreliable.

Cardiac output. Cardiac output is decreased in congestive failure except in diseases characterized by increased output (anemia, beri-beri, Paget's disease, arteriovenous fistulae, patent ductus arteriosus, and some cases of chronic cor pulmonale). In these diseases, car-

diac output is elevated when the heart is efficient. Even if diminished, in comparison with previous figures, cardiac output may still be higher than average when heart failure occurs. In any form and type of heart failure, measurement of cardiac output gives an exact evaluation of myocardial insufficiency, only if the data are compared with those preceding failure. The direct method, based on Fick's principle, is exact, but requires a complex technique including pulmonary artery catheterization. The indirect method, based on the study of respiratory exchanges as described by Haldane and Grollman, is not reliable in heart failure because of dyspnea and restlessness. The methods based on the study of the pulse wave are unreliable. The determination by means of the ballistocardiogram still requires improvement. Therefore, measurement of cardiac output is not currently used in heart failure.

Cardiac Catheterization

Cardiac catheterization. This procedure supplies exact data concerning the pressure existing in the different sections of the right heart. *Left* heart failure is accompanied by increased diastolic pressure in the left ventricle (which cannot be measured in clinical cases), increased left atrial and pulmonary arterial pressures, and an increased systolic with normal diastolic pressure in the right ventricle. The gradient between pulmonary arterial and pulmonary "capillary" pressure is normal. *Right* heart failure is revealed by an increase of diastolic pressure in the right ventricle and in a later stage by increased right atrial pressure. Cardiac catheterization is a complex procedure which is not suitable for the routine study of the cardiac patient and which may entail some risk in patients in failure. Therefore, any study in such cases should be discouraged.

Roentgenology. X-ray examination of the heart is helpful for the diagnosis of failure. Fluoroscopic examination should be performed routinely in cardiac patients. The vascularization of the lungs is observed and the size and shape of the various heart chambers is evaluated. Serial chest films may reveal a progressive enlargement of the heart or of one of its chambers.

Radiocardiography[7] reveals typical patterns in congestive heart failure: the R-wave (due to passage of a radioactive substance through the right ventricle) has a slow rise and is partially or completely fused with the L-wave (due to the passage of the isotope through the left ventricle). Isolated failure of the left ventricle is revealed by extremely slow return of the tracing to normal after the L-wave. This technique is not yet commonly used but is likely to become more and more a part of the routine cardiac work-up, at least in the hospitals. It is harmless and well-tolerated.

DIFFERENTIAL DIAGNOSIS

While a great number of conditions can simulate heart failure, some of them should be particularly kept in mind.

(a) *Lack of training* in obese persons should be differentiated from heart failure. The history and physical examination, the x-ray, and the electrocardiogram may exclude hypertension or heart disease; normal circulation time and normal venous pressure further exclude heart failure.

(b) *Neurocirculatory asthenia* and, in general, *cardiac neuroses* are revealed by a characteristic behavior, a typical appearance of the patient, and the frequent sighing respiration. Fatigability, dyspnea, or tachycardia may not be due to heart failure if physical examination, x-ray, and electrocardiogram reveal no evidence of organic heart disease; or if, in the presence of actual cardiac disease, there is a disproportion between the symptoms and the evidences of disease. In doubtful cases, circulation time is of help.

(c) In *pregnancy,* dyspnea, orthopnea, tachycardia, and dependent edema can occur without heart failure; cardiac enlargement can be simulated by displacement of the heart, and a systolic murmur is often present. If a pregnant woman has heart disease, this is either a rheumatic valvular lesion or hyper-

tension. Any apical diastolic murmur (to be distinguished from a third heart sound) should be considered pathological. Cardiac enlargement, congestion of the cervical veins, severe tachycardia or atrial fibrillation, or definite elevation of the blood pressure may reveal a cardiovascular abnormality. High venous pressure or prolonged circulation time reveal failure.

(d) In severe *anemia*, exertional dyspnea, tachycardia, dependent edema, and cardiac enlargement are common. In cases of sickle cell anemia, the liver is also enlarged. Heart failure is excluded by the absence of orthopnea, pulmonary congestion, engorgement of the systemic veins, and increased venous pressure.

(e) *Cirrhosis of the liver* causes ascites, dependent edema, and possibly exertional dyspnea, and rarely orthopnea. In cases of heart failure, edema precedes ascites, while the opposite occurs in cirrhosis. Circulation time is normal and venous pressure is decreased in cirrhosis.

(f) Differential diagnosis from *nephrosis* is easy because, in this disease, the heart is not involved. In *glomerulonephritis*, the findings in the urine and blood are characteristic.

(g) *Varicose veins* can be easily detected. In such cases, the liver is of normal size, and there is no congestion of the cervical veins.

SUMMARY

(1) While congestive failure may be obvious, in certain cases recognition of the cause of congestion may be difficult.

(2) The symptoms and signs of congestive failure are discussed. The various types of dyspnea (paroxysmal nocturnal dyspnea, acute pulmonary edema, orthopnea), cough, hemoptysis, weakness, abdominal pain, and oliguria are discussed.

(3) Weight changes, cyanosis, changes of the pulse, and pulmonary or pleural disturbances, may be caused by heart failure.

(4) Enlargement of the heart, triple rhythm, loud P_2, and systolic and diastolic murmurs may be the result of cardiac failure. The same is true of basal rales, enlargement of the liver, ascites, and gravitational edema.

(5) The various circulation time tests are discussed. Their technique is described.

(6) Clinical determinations of venous pressure and vital capacity are important for the evaluation of the severity of heart failure.

(7) Several laboratory methods supply data which are important for the diagnosis of heart failure. They include determination of cardiac output, catheterization of the heart, roentgenology, and radiocardiography.

(8) The differential diagnosis between heart failure and other conditions which simulate this picture is briefly outlined.

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SYMPOSIUM ON CARDIAC DISEASES:

III. CARDIAC FAILURE

Treatment

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While the primary defection in chronic congestive heart failure is in the functioning of the heart as a pump, numerous other concomitant physiologic aberrations, which are apparently secondary, are constantly being recognized. While specific therapy for improving cardiac function is available and is always employed, it never can completely restore this function to its normal state. For this reason treatment must also be directed towards some of these secondary physiologic abnormalities. At the same time, we have learned that other secondary manifestations are best left uncorrected, or only partially corrected, since they are in effect adaptive to the highly complex abnormal state recognized as chronic congestive heart failure.

It is important to emphasize that there is no "routine treatment of the failing heart." Each therapeutic measure must be used in conjunction with all other therapeutic measures in a highly individualized fashion. These should be appropriate for the multiple variations present in patients with congestive failure of varying degrees and due to varying causes.

Because our therapy is to be guided by numerous clinical and laboratory observations of this very complex abnormal state, it is necessary that these observations be recorded carefully and regularly in such a way that relationships between them will be readily discernible. These will include the daily recording of symptoms and signs, the weight of the patient obtained before breakfast, urine output, salt intake, drug administration, blood electrolytes and chemistries where indicated, and in some cases special tests such as venous pressure and circulation time.

REST

The most obvious way to reduce the discrepancy between the heart's performance as a pump and the metabolic requirements of the body for blood, is to reduce body activity by prescribing rest. Most cases should be severely restricted, particularly in the early weeks of therapy. However, this usually does not mean "absolute bed rest." The recumbent position in congestive heart failure has many disadvantages. Redistribution of edema fluid from the lower extremities may occur so that pulmonary congestion and pleural transudation may appear where previously absent. The recumbent position also means an increased venous return to an already overloaded heart. For these reasons, the use of a bedside lounge chair with wide arms, during the day, is often the most comfortable position for the patient. In some cases the patient may even prefer to sleep in such a chair. However, for most patients sleeping is most comfortable in a bed. The use of a back rest to elevate the upper half of the body may do much to prevent attacks of paroxysmal nocturnal dyspnea. Better yet one might use a special cardiac bed which maintains elevation of the upper part of the body and knees, so that slipping into the recumbent position during sleep is prevented.

Bedside Commode Preferred

In almost all cases the use of a bedpan on a chair or the use of a bedside commode is preferable to the use of a bedpan in bed. It has actually been shown that despite the mild exertion of getting in and out of bed with the aid of a nurse, the use of the bedside commode requires much less energy than does the use of a bedpan in bed.

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It is well-known that sustained emotional tension or periodic emotional crises can put tremendous demands on the work of the heart, by increasing both cardiac output and peripheral vascular resistance. For these reasons all attempts should be made to ensure emotional serenity. The physician can do much in this regard by allaying anxiety, screening visitors, and developing a relationship with the patient which will be supportive during the period which is truly critical. While all sedatives and hypnotics have antidiuretic effects in a patient who has not yet developed tolerance to them, and so may act counter to some of the other therapeutic measures employed, they nevertheless are usually indicated because of their more important effect on the emotional state of the patient. The opiates may be necessary if the patient is very anxious. However, milder sedation such as the barbiturates and chloral hydrate should be employed as soon as possible. Hypnotics for sleep are frequently indicated. Very soon after initiation of treatment, controlled reading, listening to the radio, or watching television may be preferable to the enforcement of complete immobility with fixation on four walls and a ceiling.

Eventually, when warranted by improvement, increase in activity is permitted. This should be graduated according to the clinical observation of the patient's response.

DIGITALIS

Digitalis is almost always indicated in the treatment of congestive heart failure. Digitalis has been shown to markedly improve the contractility of the myocardium, thus increasing the force of systolic contraction. While there has been considerable controversy regarding its ability to improve the mechanical efficiency of the heart, in some as yet unknown way it does facilitate the release of energy by the contracting myocardium. Because of the ability of digitalis to depress conduction through the atrioventricular node, the drug produces marked slowing of the rapid ventricular rate usually present in auricular fibrillation (as well as in auricular flutter and supraventricular tachycardia), thus improving cardiac performance. The action of digitalis on slowing the heart rate in congestive failure with sinus rhythm is less striking, and is due to vagal reflexes resulting mainly from the improvement of the congestive failure. Nevertheless, digitalis is extremely valuable in the treatment of congestive failure with sinus rhythm.

Characteristic of all of the digitalis preparations is the relative proximity of the toxic and therapeutic dose. This fact strongly influences the dosage and method of administration of the drug. For all of the digitalis, or digitalis-like drugs, it is necessary that the patient be given a certain amount of the drug, known as the digitalization dose, to achieve the required effect. Then, to maintain this effect, a small amount, the maintenance dose, must be given, usually daily, to replace that portion of the drug which has been excreted. The digitalization dose will depend on the type of digitalis administered. For any given preparation only approximate values can be stated as the amount likely to achieve digitalization without toxic effects. The response of any patient to digitalis is a highly individual one, so that no rule of thumb can be applied to dosage. It is therefore usually unwise to attempt single dose digitalization, since it would not produce complete digitalization in some patients and may cause serious toxicity in others. It is preferable to give a relatively large proportion of the amount known to be proper in the average case, and then to give small amounts at intervals until digitalization is achieved. It should be axiomatic that these later increments should never be given at intervals of time shorter than that required for the appearance of the maximum effect of that particular digitalis preparation.

Criterion of Response

When can one assume that full digitalization has occurred? Where auricular fibrillation is present, the ventricular rate is an excellent guide. Where sinus rhythm is present, the point of full digitalization should be determined by what is known about the usual amount re-

quired for digitalization, and by achievement of the desired effect. Only when the response of the patient to therapy appears inadequate should digitalis administration be pushed to the point of minor toxicity, and then it should be reduced to an adequate maintenance dose. When this latter technique is employed, the patient should be followed very closely clinically and electrocardiographically.

There are many types of digitalis preparations available. In general, the speed with which they begin acting is closely related to their rate of dissipation. It is preferable to select one or two drugs each, of the rapid and of the long acting preparations, and becoming familiar with their use, attempt to use only these drugs.

Slowly Excreted Preparations Preferred

The slowly excreted digitalis drugs are usually preferable in most cases, because maintenance is easier than with the more rapidly excreted group. The maintenance dose in this group is a small fraction of the amount required for digitalization, as would be expected, since the drug is slowly dissipated. Examples of this group include *digitoxin,* which takes the longest to be excreted, powdered *digitalis leaf,* and amorphous *gitalin.* For example, if digitalization need not be achieved very rapidly, an initial dose of 0.4 mg. of digitoxin may be given, and then 0.2—0.4 mg. may be given every eight hours until about 1.2 to 1.6 mg. have been administered. The patient may then be placed on the maintenance dose, which is usually about 0.15 mg. daily. Digitoxin may be given orally or intravenously; and an intramuscular form is now also available. The dose for digitoxin is the same, regardless of the route of administration. At any time one may change to the powdered digitalis leaf, which is now available in a reliable form, standardized by biological assay so that 0.1 Gm. is equivalent to one Cat Unit. This drug is dissipated more rapidly than digitoxin, and the usual maintenance dose is 0.1 Gm.

The rapid acting digitalis preparations are usually less convenient for maintenance, since they are very rapidly excreted. Examples of such drugs include *strophanthin K, ouabain, lanatoside C (Cedilanid),* and *digoxin.* These are all administered intravenously, except for the last, which is absorbed in a constant enough manner to be given orally. As would be expected, the maintenance dose of this group is a larger proportion of the digitalization dose than in the more slowly excreted drugs. They are indicated where the congestive failure is more severe and where quicker action is therefore necessary. They are useful when the amount of the drug to be given is close to the toxic level, since should toxic symptoms appear, they will be rapidly excreted when their administration is stopped. For this same reason they are useful when one desires to give more digitalis rapidly to a patient who has been receiving an indeterminate amount of digitalis, who has no signs of digitalis toxicity, who is in severe left ventricular failure, and in whom one suspects inadequate digitalization. In such a case one may give 0.4-0.8 Gm. of Cedilanid intravenously.

Digitalis Toxicity

Of paramount importance in the use of digitalis is the constant watchfulness against digitalis toxicity. In most cases, digitalis toxicity is due to overdosage. However, it is also known to occur more readily in severely damaged hearts, and especially after potassium depletion which may follow intense mercurial diuresis or resin therapy. A state of potassium depletion may exist within the myocardial cell in the absence of hypokalemia.

The subjective manifestations of digitalis toxicity include the development of a depressed mood, loss of appetite, and nausea and vomiting. While these are frequently the earliest signs of digitalis toxicity, they often do not occur at all, and then the first sign of digitalis toxicity may be one of the more serious objective manifestations. The latter include the effect of digitalis in increasing the irritability of ectopic foci in the heart, leading most frequently to ventricular premature systoles. Unless very

frequent, as in bigeminal rhythm, they rarely affect cardiac function seriously. Their importance lies in the fact that their presence frequently heralds the development of paroxysmal ventricular tachycardia, and the very serious ventricular fibrillation. Digitalis may also cause varying degrees of atrioventricular block. Indeed, almost any arrhythmia can be caused by digitalis.

Electrocardiographic Changes

It is well-known that the administration of digitalis has certain very definite effects on the contour of the ST-T complex of the electrocardiogram. While there is a very rough correlation between the amount of digitalis given and the ST-T changes, these changes may appear after only a minimal amount of digitalis, or may fail to appear even after toxic effects (on rhythm and conduction) have occurred; they frequently are present before the full therapeutic effect is achieved. Their presence is not an indication to stop digitalis.

Prophylaxis of digitalis toxicity includes careful administration of the drug during the digitalization period and frequent observation to ensure that the maintenance dose is proper. In all cases, every attempt should be made to avoid hypokalemia, which predisposes to the development of ectopic rhythms. The development of toxic effects (subjective or objective) are an indication to stop digitalis administration until enough has been excreted and the toxic effects disappear. Paroxysmal ventricular tachycardia is a serious arrhythmia and should be treated immediately with quinidine or procaine amide (Pronestyl); ventricular premature systoles if frequent should be treated similarly. Frequently congestive failure, with its effect on the myocardium, will be responsible for the presence of premature systoles. In such cases, giving digitalis and thereby improving cardiac performance will frequently cause these premature systoles to disappear.

Gitalin

Recently, interest has been awakened in gitalin, which is one of the glycosides of *Digitalis purpurea*. It is now available in the amorphous form which is stable and uniform. It is dissipated from the body at a rate between that of digoxin and digitalis leaf. Studies in the last four years have shown that there is a wider range between its therapeutic and toxic dosage than any of the other digitalis preparations. For digitalis leaf, digitoxin, or digoxin the therapeutic dose necessary to achieve digitalization is approximately two-thirds of the toxic dose. With gitalin the therapeutic dose is approximately one-third of the toxic dose. It will take several more years of wide use before this can be considered to be completely substantiated. However, where toxic effects appear early in the use of the other digitalis preparations, so that the therapeutic range of dosage cannot be reached, it may be well worth while to use gitalin. The average maintenance dose is 0.5 mg.; the average digitalizing dose is 6.0 mg. Necessary still, are all the precautions of individualizing dosage and observing the patient carefully. However, in most cases, if the patient is on a maintenance dose of 0.15 mg. of digitoxin or 0.1 Gm. of digitalis leaf, he may be transferred to 0.5 mg. of gitalin.

If digitalization is once indicated, should the drug ever be discontinued? The indications for permanent digitalization will depend on the etiology of the congestive failure. If the basis of the congestive failure is a temporary diseased state, digitalis should be given only while this diseased state impairs cardiac function to the point of congestive failure. On the other hand, if the primary cause of the congestive failure is permanent and relatively unalterable, digitalis should be continued for life. Examples of the first type of case include acute myocarditis, or the rapid ventricular rate associated with a paroxysmal supraventricular arrhythmia; examples of the second type of case include chronic rheumatic, arteriosclerotic, or hypertensive heart disease.

SALT RESTRICTION

One of the most significant advances in the management of chronic conges-

tive heart failure in the past fifteen years has been the discovery of the value of salt restriction. Therapeutically this method has been of great value, even though all the actual pathologic mechanisms responsible for salt and water retention in congestive heart failure are as yet imperfectly understood.

Restriction of salt should be more marked in the early phases of treatment, when only 0.5 Gm. of sodium per day should be permitted. Even though there is good evidence that in chronic congestive failure there is some primary water retention, unrelated to sodium retention, practically it has not been found necessary to restrict fluids in most cases. The patient may be permitted 2000 - 3000 cc. per day. However, the administration of large volumes of water as recommended by Schemm is unnecessary and often dangerous.

If the patient maintains his "dry weight" with an increase in physical activity, the amount of salt in the diet may also be increased, but rarely above 1.5 Gm. of sodium per day.

Enforcement of this regime at home implies that no salt be used in cooking, the omission of salted foods, the use of "salt free" bread, unsalted butter and canned goods, and the avoidance of food made with baking powder. In addition, medicine containing sodium must be eliminated by the physician. Ingenuity in the preparation of food, such as the use of garlic, condiments, lemon juice, wine, and salt-substitutes, often helps in making the food interesting.

Refractory Cases

In refractory cases, it is sometimes necessary to reduce the sodium intake below 0.5 Gm. per day. To achieve this, one must resort to a diet difficult to maintain, or restrict food intake to Lonalac Formula (400 cc. five times daily) and 250 cc. of orange juice twice daily. Such a regime should not be enforced for more than one week.

In some cases where strict sodium restriction cannot be maintained, the use of cation exchange resins has been of value. These resins withdraw sodium and other electrolytes from the gastrointestinal tract. Combinations of resins containing some potassium and a small percentage of anion exchangers must be used. However, these resins are not efficient unless the sodium content of the diet is restricted to at least two grams per day; their use therefore does not permit unrestricted salt intake. They have not proven as useful as initially hoped, the disadvantages of their use being the disagreeable gastrointestinal effects which they frequently produce, and the danger of developing serious electrolyte imbalance.

In all cases of salt restriction, especially if the resins are also being used, certain precautions should be taken. The diet should be so constructed as to avoid the development of hypoproteinemia. It is usually wise to prescribe the daily use of a multivitamin preparation. During periods of unusual salt loss, as during hot weather, adjustments in the diet should be made. The administration of two glasses of orange juice daily will usually protect against potassium depletion. Symptoms and signs of electrolyte imbalance should constantly be watched for, and the serum electrolyte concentration studied when indicated.

DIURETICS

Marked diuresis and loss of weight often result merely from administering digitalis and enforcing rest. Usually, however, use is also made of the mercurial diuretics. These drugs interfere with the reabsorption of chlorides in the renal tubules. This increased excretion of chlorides carries off fixed base (chiefly sodium, but also potassium and calcium) and water.

Various types of mercurial preparations are available (some with theophylline and some without) for intramuscular administration. Mercaptomerin (Thiomerin) may be injected subcutaneously. This is advantageous because the injection may be made in the deltoid region where edema is less marked and absorption, therefore, more rapid. Mercaptomerin may also be injected by the patient himself. These drugs rarely should be injected intravenously, and then only well-diluted and very slowly, since this

route has been reported to cause fatalities. An oral mercurial is now available which is often useful when the patient is ambulatory; when taken, it often reduces the required frequency of injections, or may even supplant them. However, this oral form may produce gastrointestinal symptoms and mercury poisoning. Oral mercurials should therefore be used on some intermittent basis: every other week, or for only four days a week with a three day rest period.

Rule Out Idiosyncrasy

The initial dose of the mercurial should be a small one (usually 0.5 cc.), in order to evaluate the patient's response and to rule out idiosyncrasy to the drug. Injections should be given at proper intervals, every one to three days, to permit a gradual loss of weight, preferably not more than five pounds in twenty-four hours. Too rapid and massive diuresis may lead to potassium depletion with its predisposition to digitalis toxicity, other forms of electrolyte imbalance, muscle cramping, and may favor the development of phlebothrombosis. To avoid nocturnal polyuria, it is advisable to give the injections early in the morning. The frequency of future injections will depend on the patient's condition and especially his weight from day to day. Ten pounds of occult edema may be retained without clinical signs. If possible, one should prevent retention of water beyond an amount that can be removed by a single mercurial injection.

Contraindications

Contraindications to the mercurial diuretics include the presence of acute renal disease, such as acute glomerulonephritis, and chronic renal disease with moderately marked insufficiency (serum urea nitrogen over 60 mg./100 cc.). The failure of an edematous patient to respond to repeated injections becomes a contraindication to more injections until serum electrolytes are studied and renal function is evaluated.

Ammonium chloride, which has mild but definite diuretic properties when given alone, is useful in potentiating the action of the mercurials. In addition, it prevents hypochloremia, a state which reduces or prevents mercurial diuresis. It should be given in the form of enteric-coated tablets in doses of 6.0 Gm. daily for two to three days preceding and during the day of the mercurial injection. In spite of their reputation, the type of enteric-coated tablets available today usually do disintegrate in the gastrointestinal tract, and only rarely cause nausea. If it is to be used over a long period of time, ammonium chloride should be given intermittently, five days per week, or every other week, although this precaution against hyperchloremic acidosis is probably necessary only in patients with renal impairment.

Diamox

Recently a new diuretic, which is a carbonic anhydrase inhibitor, has been introduced under the trade name of Diamox. This enzyme inhibitor slows the formation of carbonic acid from carbon dioxide and water in the kidney, resulting in the loss of bicarbonate ion in the urine, which carries with it sodium, potassium, and water. Thus there is diuresis with an alkaline urine. Since it acts differently from the mercurials, which increase the excretion of chloride ion, it may be given with the mercurials. Ammonium chloride appears to block the diuretic effect of this drug and should not be administered at the same time. Diamox is given in doses of 250 mg. a day. Administered alone, it is not as effective as the mercurial diuretics. Other diuretics such as the xanthines (theophylline especially) and urea have been used, but have only limited value.

ELECTROLYTE IMBALANCE

Serious derangements in the fluid and electrolyte compartments in the body are most likely to occur where prolonged salt restriction, mercurial diuresis, and exchange resin therapy are applied too strenuously, and especially when applied in combination. Associated renal disease is also a very important predisposing condition.

Suspicion of the presence of electrolyte imbalance should be aroused when the diuretics become ineffective in the

face of increasing signs of congestive failure (decrease in urine volume and increase in body weight), and when any of the following signs and symptoms appear: asthenia, tachycardia, headache, anorexia, lethargy, thirst, nausea and vomiting, giddiness, muscle or abdominal cramps, and delirium. The type of electrolyte imbalance present is determined by serial electrolyte studies and a careful review of the preceding therapy.

Low Salt Syndrome

Low salt syndrome: This is usually a depletion state arising from prolonged marked salt restriction, usually in addition to intensive mercurial diuresis. Serum sodium, chloride, and CO_2 combining power are low, serum urea nitrogen is frequently elevated, and the urinary chlorides are very low or absent. The prognosis is grave; untreated, there is progression to shock and death.

Treatment is by the administration of salt. Early this may be given orally in tablet form or in soups. If the condition is severe, 5% NaCl must be given intravenously. Many methods have been described for estimating the amount of salt to be given. These methods range from calculations depending on the weight of the total body water or the weight of the extracellular fluid, to a rough rule stating that one to three grams of NaCl will be needed to raise the serum sodium concentration one milliequivalent per liter. All of these calculations involve many unfounded assumptions, among which is the concept that the hypotonicity produced by the sodium deficit is of the same degree in the intracellular fluid as in the extracellular fluid. For these reasons, it is best to proceed slowly, never exceeding 300 cc. of 5% NaCl in twenty-four hours, and always being guided by the clinical state of the patient, as well as by laboratory determinations. Usually much less salt than expected will be needed before diuresis and improvement in symptoms occurs. Because of a frequently associated potassium deficit, it is also advisable to give two to three grams of potassium. Thirst continues and is often severe when hypertonic salt is given, even when the serum sodium is still low.

Frequently, if attempts are made to restore normal serum electrolyte concentrations too quickly, the patient develops severe pulmonary edema; one is then confronted with a moribund patient with normal serum electrolyte values. Moreover, even when carried out under the best conditions, the therapy outlined above will unfortunately fail to save the patient. The reason for this is that the Low Salt Syndrome often cannot be distinguished from *chronic dilution hyponatremia*. The latter condition may delop in patients with untreated severe congestive failure, as well as in those who have been treated vigorously with salt restriction and mercurials. These patients usually do not complain of the symptoms described for those with the Low Salt Syndrome. Chronic dilution hyponatremia is apparently not an acute depletion syndrome, but appears to be related to some profound interference with water excretion and changes in intracellular osmolarity. It is of very erious prognostic import. The administration of salt to these patients is not helpful, and often hastens death.

Hypochloremic Alkalosis

Hypochloremic alkalosis: This condition is usually due to intensive mercurial diuretic therapy causing a relatively greater loss of chlorides than sodium. When the serum chloride falls low enough, all of the chlorides are reabsorbed by the tubules, and diuresis will not occur. Where there has been a poor food intake or a loss of chlorides by vomiting, this syndrome is more likely to occur. The serum electrolytes will be as follows: serum chlorides low, serum sodium normal or slightly reduced, serum potassium usually reduced, serum CO_2 combining power increased, and serum urea nitrogen often elevated. Treatment is by the administration of ammonium chloride in *non*-enteric coated tablets. If the patient cannot tolerate oral ammonium chloride, it may be given intravenously in a 1% solution—slowly, or twenty cc. of 10% HCl may be given in 600-1000 cc. of water orally in divided doses. This condition may be prevented if ammon-

ium chloride is used routinely with the mercurials.

Hypokalemia and Hypocalcemia

Hypokalemia and Hypocalcemia: Both potassium and calcium are lost as fixed base when mercurials are administered. Hypokalaemia may result from insufficient dietary intake while intensive mercurial diuresis is enforced. It is frequently associated with hypochloremia and hyponatremia. It is especially likely to occur with intensive resin therapy, since some potassium loss continues, even though potassium-containing exchangers are added to the resin mixture. The condition can frequently be recognized by the rather specific electrocardiographic changes which occur. Besides the serious clinical symptoms resulting from hypokalemia, the condition favors the cardiotoxic effects of digitalis. It may usually be prevented by the routine administration of two glasses of orange juice daily. Therapy of the condition includes the administration of potassium orally, two grams four times daily, potassium chloride if hypochloremic alkalosis is present, and potassium citrate or acetate if acidosis is present. Hypocalcemia usually arises from the prolonged use of cation exchange resins, especially the sulfonic forms. Clinical tetany does not appear because of the usually associated hypokalemia and acidosis, both of which protect against tetany.

Hyperchloremic Acidosis

Hyperchloremic acidosis: This serious disturbance has been observed in patients in congestive failure with renal disease who daily receive ammonium chloride, in occasional cases as little as six grams for eight days. These patients, because of an impaired renal capacity to produce ammonia and to excrete maximally acid urine, lose much fixed base. The clinical picture includes lassitude or stupor, Kussmaul breathing, elevated serum chlorides and serum urea nitrogen, and low serum CO_2 combining power. Because it is common to have mild albuminuria, cylindruria, and azotemia in congestive failure, it is often difficult to determine the presence of a serious renal disorder. If there is marked persistent albuminuria, low fixed urinary specific gravity, and if the serum urea nitrogen is over 65 mg./100 cc., one should seriously consider the presence of intrinsic renal disease. In such cases, this complication can be prevented if ammonium chloride is given only three days per week, and if electrolyte studies are done periodically. Treatment of the condition involves the administration of oral sodium bicarbonate or intravenous one-sixth molar sodium lactate solution, such therapy always being guided by frequent electrolyte studies.

Serum Electrolyte Studies

While serum electrolyte studies are of the greatest value in detecting and following the treatment of the above conditions, such studies do not disclose the multifaceted aspects of electrolyte imbalance for the following reasons:

1. The concentration of an ion in the serum does not always reflect the total store of this ion in the body.

2. These studies do not give us sufficient information about the intracellular concentration of the ion, and especially give us no information about intrinsic changes in intracellular osmolarity. Even complicated balance studies have not given us this information.

3. The amount of total body fluid and the proportions present in the various compartments of the body are not determined by these measurements.

4. Finally, of great importance is the fact that the internal environment of a patient with chronic congestive heart failure is greatly changed from the normal. Such absolute abnormalities in serum ion concentration as we may find in these patients, may be adaptive through the operation of unknown homeostatic mechanisms stimulated by the primary abnormalities resulting from the failing heart. These tertiary or adaptive mechanisms include such as yet imperfectly evaluated factors as the secretion of antidiuretic hormone, primary water retention, and the action of "volume receptors."

OTHER MEASURES

Where pleural effusions are present and dyspnea is severe, thoracentesis is indicated. Abdominal paracentesis may become necessary, especially in patients with tricuspid valvular disease or a constrictive pericardium. Since the introduction of mercurial diuretics and salt restriction, the use of Southey tubes to drain off edema from the lower extremities is rarely necessary.

There is no doubt that thromboembolic phenomena occur with greater frequency than normal in chronic congestive heart disease. However, the routine use of anticoagulants (dicoumarol or heparin) has not yet been proven justifiable. Anticoagulants are indicated, however, if actual signs of phlebothrombosis of the deep veins of the legs appear, if a recent myocardial infarction is present, and probably where auricular fibrillation of recent origin occurs. It should be remembered that severe hepatic congestion may itself reduce prothrombin concentration significantly, and make the patient unusually sensitive to dicoumarol. In all cases where adequate laboratory facilities are not available to follow the effects of anticoagulants, these drugs are best omitted from the therapeutic regime.

In some cases of refractory chronic congestive failure the use of radioactive iodine has been recommended. A large single dose sufficient to produce myxedema is given. Later, small doses of thyroid are given with the purpose of maintaining a mild or moderate hypothyroid state, in which there should occur a reduction in the metabolic requirements of the body as well as of the heart muscle itself. This method, while apparently of some benefit in isolated cases, has yet to be further evaluated. Its use in coronary sclerotic heart disease with severe angina pectoris seems to be more promising.

TREATMENT OF ACUTE LEFT VENTRICULAR FAILURE

Patients while under apparently satisfactory treatment for chronic congestive failure may rather suddenly develop an exacerbation of their failure, mainly left-sided, with the alarming symptoms associated with pulmonary congestion and edema, bronchospasm, and acute anoxia. This requires the immediate institution of measures to reverse this acute picture.

One of the most vicious symptoms of acute left heart failure, and usually induced by the sudden onset of dyspnea, is severe panic. This results in an increase in the demands on an already overtaxed heart. By increasing the work of the heart, the discrepancy between its oxygen needs and its supply is frequently increased; it also predisposes to the potentially dangerous ectopic rhythms. Nothing is more effective in combating this detrimental emotional state than a calm, reassuring attitude on the part of the physician and the liberal use of opiates, intravenously if necessary.

Oxygen Therapy

Oxygen therapy is of great value, especially if there are signs that pulmonary edema is developing. Since high concentrations of oxygen are desired, a mask is the preferred method of administration. If uncontrollable fear develops in the patient because of the mask, a tent or nasal catheter may be substituted, although this results in the delivery of a lower concentration of oxygen. Oxygen under pressure is even more valuable; in most institutions the simplest method of administration is by the meter mask, where a positive pressure, up to four centimeters of water, is produced during expiration. Oxygen under pressure provides a direct opposing pressure to the external surfaces of the pulmonary capillaries, maintains greater patency of small bronchi during expiration, and reduces the return of blood into the right heart and lungs. More efficient, but less often available are such devices which permit intermittent positive pressure breathing or continuous pressure breathing. All forms of pressure breathing are contraindicated in the presence of cardiogenic shock, since by reducing the return to the left ventricle, they would further reduce cardiac output. The use of alcohol vapor mixed with the oxygen, because of its antifoaming action, is also of value in treating pulmonary edema.

Even though the patient is already on digitalis, the development of acute left heart failure should at least suggest the possibility that he is not adequately digitalized. More digitalis may be indicated. A quickly excreted type is preferable so that should toxic signs develop, they will be of short duration. The problem of dosage will be facilitated if the patient has auricular fibrillation, since then the ventricular rate may act as a control. 0.4 to 0.8 mg. of Lanatoside C may be injected intravenously.

Aminophylline

Aminophylline is a very useful drug for relief of the dyspnea, accomplishing this mainly by its bronchodilating action. It is most effective when administered intravenously (slowly and well-diluted), but is also valuable when given rectally; it is too painful when given intramuscularly, and of little use when given orally. It should not be used intravenously if there has been a marked drop in blood pressure.

Bloodless phlebotomy is often a helpful adjunct. It is accomplished by applying blood pressure cuffs to all four extremities. Three of the cuffs are inflated at a time to a pressure slightly lower than the patient's diastolic pressure. Each cuff is released in rotation every fifteen minutes, three cuffs being inflated at all times. Venesection, while rarely indicated, if performed rapidly, with at least 500 cc. of blood being removed, may be spectacular. Both procedures are contraindicated if cardiogenic shock is present.

One should always attempt to ascertain why the episode of acute left heart failure occurred. Did the acute heart failure occur because the therapeutic regime for the chronic congestive failure was inadequate? Or did some new complication precipitate the episode: acute myocardial infarction, acute myocarditis, or an acute emotional crisis? One must also rule out conditions which might simulate acute left heart failure: pulmonary embolism, acute pneumonitis, pulmonary atelectasis, and spontaneous pneumothorax. Cheyne-Stokes breathing due to anoxia or excessive sedation may waken the patient at night and simulate paroxysmal nocturnal dyspnea.

THERAPEUTIC IMPLICATIONS OF THE ETIOLOGY OF THE HEART FAILURE

In all cases of chronic congestive failure, the specific etiology of the heart failure will frequently have a very profound influence on the therapy.

If hyperthyroidism is present, treatment will often prove ineffectual if this abnormal state is not corrected. It is often difficult to evaluate the presence of this condition, since the basal metabolic rate is frequently elevated in congestive failure without thyroid dysfunction; even radioactive iodine uptake by the thyroid may be abnormally high if the patient has been on a salt restricted diet, since such diets are also very low in iodine. Careful clinical studies and a serum protein-bound iodine determination will help make the diagnosis under these circumstances. If the situation remains doubtful, the patient should be given the benefit of the doubt. Antithyroid drugs and iodine should then be used as a therapeutic trial.

The presence of a recent myocardial infarction will not contraindicate the use of digitalis, but may make one slightly more cautious in its use because of the possibility of ectopic rhythms arising in the ischemic zone adjacent to the infarct. Serial electrocardiograms should be taken more frequently in such a case, and the period of rest may be prolonged.

Arrhythmias

Arrhythmias associated with congestive failure must be evaluated, and indeed may be found to have been responsible for precipitation of the congestive failure. If paroxysmal supraventricular tachycardia, auricular flutter, or auricular fibrillation exist with congestive failure, it is wiser to slow the ventricular rate adequately with digitalis, before using such drugs as quinidine or Pronestyl.

If pericarditis with effusion is present, tamponade must be ruled out, since all therapeutic measures will fail unless the

pericardial fluid is removed. If a constrictive pericardium is present, a pericardectomy must be planned or a progressive downhill course will ensue.

If the congestive failure is due to chronic cor pulmonale, usually associated with severe chronic hypertrophic pulmonary emphysema, active therapy of the chronic broncho-pulmonary disease will be as important as the specific cardiac measures. The objective will be to promote better ventilation (abolish patchy atelectasis and trapping of air), improve intrapulmonary mixing, and open portions of the pulmonary vascular bed formerly collapsed, and in this way abolish the anoxia which leads to an increase in pulmonary vascular resistance. This will help greatly in reducing the load on the right heart. Such patients will thus require the use of antibiotics, bronchodilator drugs, sputum liquifiers, bronchial aspiration, avoidance of respiratory depressant drugs, facilitation of cough, and occasionally mechanical respiratory aids. Phlebotomies to reduce the secondary polycythemia may be necessary. In these cases great caution must be used in prescribing oxygen, because of the danger of depressing respiration, with resultant carbon dioxide retention and narcosis.

In rheumatic heart disease the possibility of acute rheumatic myocarditis must always be considered. Such cases do not respond as well to digitalis and may require corticotropin or cortisone therapy, especially if serious conduction disturbances or arrhythmias are present. If no rheumatic activity can be demonstrated, and if the findings indicate that a "tight" mitral stenosis is the main obstacle to adequate cardiac function, mitral commissurotomy will be indicated.

If heart failure is due to a large arteriovenous aneurysm, beri-beri, myxedema, or severe anemia specific therapy for each of these conditions is necessary before any improvement can be expected.

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EDITOR'S NOTE: Due to the length of this Symposium on Cardiac Diseases and our desire to preserve the continuity of the symposium it was felt advisable to omit the "Features Section" from this issue. This information will be published in the next issue of the QUARTERLY.

SYMPOSIUM ON CARDIAC DISEASES:
IV: ROENTGENOLOGICAL EXAMINATION IN THE DIAGNOSIS OF HEART DISEASE

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The steady, remarkable progress in the field of cardiac surgery is as much a surgical-technical triumph as it is an outgrowth of refined, more specific diagnosis in the field of congenital anomalies. It was a clinician, the recognized authority in this field, Dr. Helen Taussig, who first suggested to Blalock, the surgeon, the possibility of an operation to increase the circulation to the lungs for alleviation of pulmonary stenosis. We have come to recognize that when cardiac surgery is contemplated, the single physician should be replaced or fortified by a team consisting of the clinician, the radiologist, the surgeon, the physiologist, and the anesthesiologist. It is well-known that Dr. Taussig places great emphasis upon x-ray and fluoroscopic studies and is particularly experienced in this field. This has enabled her to collect numerous roentgenological observations, even without contrast media, which are extremely helpful in the differentiation of these malformations. Angiocardiography and cardiac catheterization permit us to assess the anatomy and physiology of the chambers of the heart and large vessels far better than by the use of the conventional x-ray film or fluoroscopic observations. However, these procedures are more often reserved for the more obscure cases.

There are anomalies which are simply demonstrated by esophageal delineation with barium or by oil bronchography, *e.g.*, vascular rings which encircle the esophagus and compress the trachea; the double aortic arch (first described by Dr. A. Arkin of our staff); the ectopic right subclavian artery passing behind or in front of the esophagus; and the anterior or posterior type of right aortic arch. It is obvious that no cardiography or catheterization is indicated before the conventional methods have been completely exhausted.

Extracardiac Pathology

It is not rare to find something on x-ray films which is in close relation to the heart, apparently part of the heart, and which may even show pulsating phenomena. These shadows, however, represent extracardiac pathology, such as a pericardial diverticulum or an esophageal mass, apparently attached closely to the heart. We know that the thymus gland, particularly in infants and children, causes great difficulty in differentiation from the heart shadow.

In adults with congenital anomalies, the roentgenological problem is much simpler. By adulthood, the heart will have reached a stage of chamber enlargement obvious in x-ray films. Or, as in the case of coarctation of the aorta, additional signs such as rib notching have developed.

The questions which can be answered by the radiologist are several. Is the heart enlarged? Is the enlargement characteristic and suggestive of a particular pathological heart type? To these we might add a third question. Is there evidence of heart failure, and if so, what particular type is prevalent? Finally, one may determine if an effusion, embolism, or infarction is visible. It is frequently important to have seriographic controls to observe the influence of bed rest and medications, *i.e.*, the regressive and receding enlargement of the heart.

Despite diaphragmatic position, heart strain, and variations of lung elasticity, we are able to establish a norm beyond which we can speak of enlargement of the heart. We have recently revised our normal standards for blood pressure in-

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terpretation in older persons and it may become necessary to revise our roentgenological nomograms after many more thousands of heart films have been better evaluated and correlated. At the present time, the nomograms of Ungerleider and Gubner of the Equitable Life Insurance Society of the United States are in general use. The usual film is taken as a teleroentgenogram at a distance of six or more feet in moderate, yet not forceful inspiration. The patient should be in an upright position as close to the film as possible. A ten per cent range of normal variation should be allowed in all calculations.

Cardiac Measurements

The first measurement to be taken is that of the transverse diameter of the heart. This is a summation of the maximal extent of the right and left heart borders from the midline. Rotation of the body is to be avoided. The formula of Hodges and Eyster is the basis of computation of the transverse diameter, which is normally given as between ten and fifteen centimeters, with an average of twelve centimeters. Enlargement to the right does not necessarily mean right heart enlargement and enlargement to the left does not always mean left heart enlargement.

The second diameter to be measured is the longitudinal diameter, *L*, which connects the point of demarcation between the right auricle and vascular pedicle to the apex of the heart. An increase in *L* is most often indicative of dilatation of the ventricles. The average length is about thirteen centimeters in normal adults. The maximum normal is fourteen and one-half centimeters.

The third diameter is the broad diameter, *B*, which is the greatest diameter perpendicular to the longitudinal diameter and normally measures between nine and ten and one-half centimeters. It is frequently divided into its two components.

Cardiac Area

Assuming that the heart has an elliptical configuration, these measurements permit us to calculate the cardiac area as $A = \pi/4 \times L \times B$. Again using the convenient nomograms for adults prepared by Ungerleider and Gubner, we read off the measured areas and compare them with the expected areas based on the weight and height of the individual. The normal average is about 112 square centimeters for males and 100 square centimeters for females. To convert these planographic measurements into volumetric approximation we need an additional lateral film which gives us lateral, *D*. The volume (*V*) equals $C \times L \times B \times D$, in which *C* is a constant, 0.53, according to Bardeen (0.63, according to Kahlsdorff). We prefer the latter constant in our own department. We have rarely found any need for a measurement of the aorta. The size of the hilar vessels is sometimes measured, and ranges between ten and fourteen millimeters, with an average of thirteen millimeters.

The cardiothoracic index as an indication of heart enlargement has been virtually discarded, since no simple relation exists between the transverse thoracic and transverse cardiac measurements. Further segmental subdivisions, as advocated by Vaquez and Bordet, have a certain didactic value but are not strictly related to anatomical chamber structures and location.

Seriographic Measurements Most Important

The shortcomings of all measurements are obvious; yet, as an index, rather than as numerical values, they are preferable to subjective estimations. They can also be recorded, thereby permitting us to compare receding or progressive enlargement from day to day and from year to year. In chronic heart disease, it is not the single examination, but the serial observations which permit us to assess the damage, the reserve available, and the prognosis. A good example of such serial radiological observations is the recent study of Jarvis and Sossman on the effect of desoxycorticosterone acetate on the heart size in Addison's disease. In this study, a heart was seen which originally was sixteen per cent below the predicted size, and which, under treatment, enlarged to nineteen per cent above the predicted size.

Heart Shapes

Besides heart size the *shape* of the heart is of great importance. We recognize four distinct radiological configurations of the heart: 1. the mitral heart; 2. the aortic configuration; 3. the combined lesion; and 4. the pericardial shape.

Angiocardiographic studies have somewhat modified our interpretation of the topography of the heart chambers (Figure 1). The right ventricle does not normally reach the right heart border anywhere in the postero-anterior view.

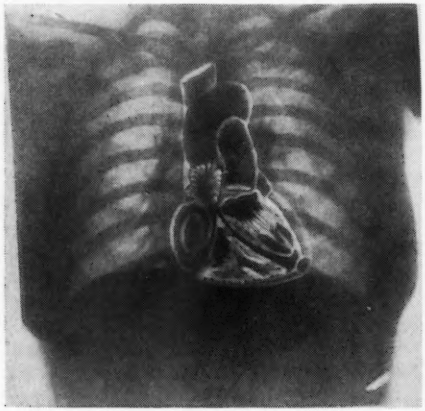

Figure 1

Topography of the heart superimposed on an x-ray film. Modifications by angiocardiography described in text.

The interventricular septum is more vertical than previously assumed. The right auricle reaches further medially on the diaphragmatic side than commonly assumed. It is obvious from such studies that the left auricle is normally hidden within the general cardiac shadow, but that the left auricular appendage, in the postero-anterior view, approaches the contour of the left heart border and frequently becomes visible under normal conditions and in mitral stenosis when auricular fibrillation or thrombosis is present.

Deductions drawn from angiocardiography as to the size of a chamber can and have been challenged. The size of the ventricle and the completeness of the outline might not be exact, since the mass of the papillary muscle and the obliquity of the ventricular septum, not to mention thrombotic material and dye dilution, may lead to deflection of the dye and incomplete filling of the ventricle.

Mitral Configuration

Of the four pathological heart types, the *mitral heart* (Figure 2) is most easily identified by the enlarged left auricle which extends first posteriorly and then laterally, either to the right (more commonly) or at times to the left. Variations might be explained by differences in thorax construction (flat chest *versus* pyknotic chest), the degree of right heart enlargement, pulsatory rotation, and the presence of a secondary pulmonary hypertension and other factors of circulatory dynamics.

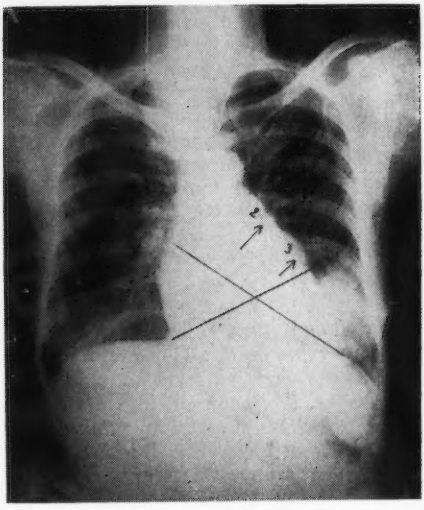

Figure 2

Mitral configuration: showing 2) prominence of the pulmonary artery and 3) prominence of the left auricular appendage. An infarct can be seen in the left lower lung field.

The enlargement of the left auricle is revealed by the displacement of the barium-filled esophagus best seen in the right anterior oblique view. Such displacement occurs in seventy-five per cent of all mitral hearts, but occurs also, to a minor degree in normal persons, and may be absent when the mitral valve is stenosed.

The visualization of a double edge or festoon on the right side, or an enlarged left auricular appendage on the left side is most frequently found in mitral stenosis and is almost pathognomonic. It is our experience that marked prominence of the auricular appendage is due to a true dilatation of the appendage and occurs most frequently in the presence of auricular fibrillation. The appendage prominence is seen in systole as well as in diastole and disappears after auricular amputation, leaving only the pulmonary artery prominent. In later stages of auricular distention, the barium-filled esophagus no longer measures the posterior enlargement of the left auricle. The esophagus slips over the cone-shaped prominence of the auricle to the right or left side and we see a moderately displaced esophagus overshadowed by the massive aneurysmal left auricular prominence.

Enormous distention of the left auricle has been found and described. Calcifications of the auricular wall or in its lumen are not rare. Other signs of mitral stenosis are widening of the angle of bifurcation of the trachea, elevation of the left main bronchus, fullness of the pulmonary artery, and bronchial compression. The enlarged right heart displaces the left ventricle posteriorly; the pulmonary conus is widened and prominent.

Summary: Mitral stenosis is usually obvious in an x-ray when several of the above mentioned features are present. Any single sign, however, may be absent. The presence of any one sign alone is unreliable. Mitral stenosis may occur without changes in the cardiac silhouette. Mitral configuration is simulated in adolescence and by a funnel shape chest deformity. In children, the esophageal displacement is frequently absent despite mitral stenosis.

Aortic Configuration

The *aortic configuration* (Figure 3) is characterized by the enlargement of the left ventricle to the left and posteriorly. The apex is rounded and is displaced outward, and frequently downward. The angle of rotation of the body necessary to clear the spine is increased beyond fifty-five degrees and gives a fair estimate of the degree of dilatation. The enlargement of one chamber frequently affects the position of another chamber.

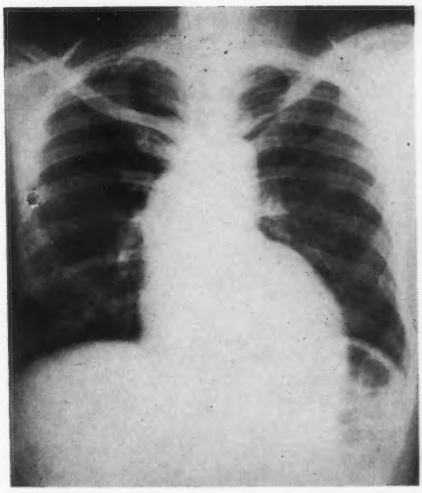

Figure 3

Aortic configuration: The boot-shaped heart with hypertrophy and dilatation of the left ventricle. Aortic insufficiency.

Angiocardiography shows an increased convexity and displacement of the interventricular septum to the right. It is most important to look for calcification of the valves in all cases of rheumatic heart disease. Sossman estimates that ninety per cent of all patients with aortic stenosis show valve calcification as compared with ten per cent in mitral stenosis. To visualize the valve the patient has to be turned into a slight anterior oblique position and penetrating films must be taken. Careful fluoroscopic examination supplemented by spot films are frequently preferable to the survey film. Calcified valves are found along the auriculo-ventricular junction line. The large calcified ring which is frequently found in older persons represents the annulus fibrosus and not the valve, and is not a sign of mitral stenosis. In differentiating between aortic stenosis and aortic insufficiency, clinical data are most important, but fluoroscopic observation will also be helpful. In aortic stenosis the contrac-

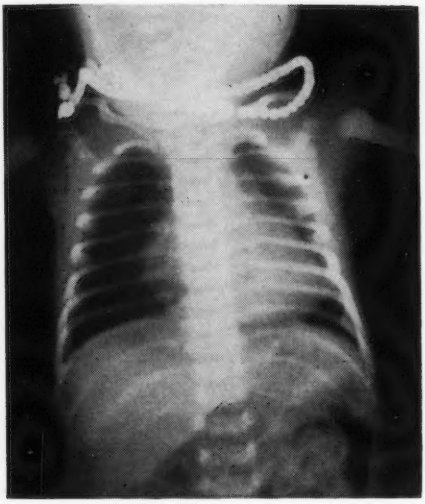

Figure 4

Coeur en sabot in the Tetralogy of Fallot. Note the ischemic lungs.

tions are slow and forceful, as compared with the pulsatory excursion in aortic insufficiency. Absence of dilatation of the aorta in the presence of a large left ventricle favors the diagnosis of aortic stenosis.

Tetralogy of Fallot

Among the congenital hearts which most closely resemble the aortic configuration is the Tetralogy of Fallot (Figure 4), which presents the characteristic "woodenshoe" (coeur en sabot) type of heart. The elevated apex indicates that the right ventricle displaces the left ventricle upwards and posteriorly. The small size of the pulmonary artery and the decreased vascular markings in the lung are further points in favor of the Tetralogy, yet a similar picture is seen in tricuspid atresia.

We, therefore, must often resort to the electrocardiogram to differentiate these conditions. The Tetralogy shows *right* ventricular preponderance, whereas tricuspid atresia presents *left* ventricular preponderance. The oblique and lateral views will also be of help in differentiation, but the electrocardiographic pattern has to be taken into consideration.

The great difficulty in the radiological diagnosis of congenital lesions by conventional films and fluoroscopy is due to the fact that the same malformation may occur with a small or large heart, a narrow or wide pulmonary artery, or a normal or wide aorta.

The Eisenmenger syndrome, for example, usually shows a "woodenshoe" type of heart, but is just as frequently found with a globular configuration. The interventricular septal defect may be associated with either a small or a large heart. Only fifty per cent of patients with a patent ductus arteriosus have a dilated pulmonary artery, and there may be a great variation in the individual chamber enlargement. It is, therefore, essential that all available data be gathered and correlated.

Combined Lesions

Combined lesions (Figure 5), such as mitral and aortic lesions, and mitral stenosis with hypertension show radiological elements of each separate lesion in great variation. An additional tricuspid lesion increases the transverse heart shadow in its right-sided component, and the esophagus is not only displaced posteriorly, but is also overshadowed by the enlarged right auricle. Its displacement to the left may be exaggerated. The

Figure 5

The combined valvular lesion in a rheumatic heart: Mitral stenosis and insufficiency and aortic valvular involvement. Findings were confirmed by electrokymography. Note the pleural effusion in the right base.

aortic configuration frequently prevails in cases of mitral stenosis combined with hypertension or aortic valvular involvement, and it often obscures the mitral component completely.

The Pericardial Shape

The *pericardial shape* (Figure 6) is a transitory shape caused by an accumulating effusion in the pericardial sac. When fluid accumulates slowly, as in tuberculosis, or rapidly, as in rheumatic fever or pneumococcal infection, the pericardium begins to stretch and balloon. It proceeds through various stages and shapes, yet the first one hundred cc. are rarely detected. Early, it is triangular and global, and later one sees a configuration which might be called "onion shaped." The longitudinal diameter approximates, or is greater than, the transverse diameter. The diaphragmatic angle is acute, and the vascular pedicle is small. All cardiac subdivisions have disappeared and the pulsations are diminished. There is no difference in density between the heart and the surrounding fluid, but there are several roentgenological methods to differentiate dilatation of the heart from pericardial effusion. The shift of the fluid in different positions, the influence of forced inspiration (Valsalva test), changes in the heart size following medication and bed rest, and observation of the esophagus and bronchial bifurcation are all of diagnostic import. Here, as elsewhere, a repeat examination at selected intervals is more informative than the single film taken as an emergency at the bedside.

On the contrary, the heart in constrictive pericarditis is abnormally small, with a decrease in pulsations best demonstrated by kymography. The presence of pericardial calcification is not always a sign of constriction of the heart. We have seen extensive pericardial calcification without the slightest evidence of cardiac embarrassment. Even in the absence of calcification, the presence of a small heart with signs of heart failure and dyspnea, and an absent aortic knob, should make one suspicious of constrictive pericarditis. Roentgenologically, as well as clinically, the results of decortication are very impressive.

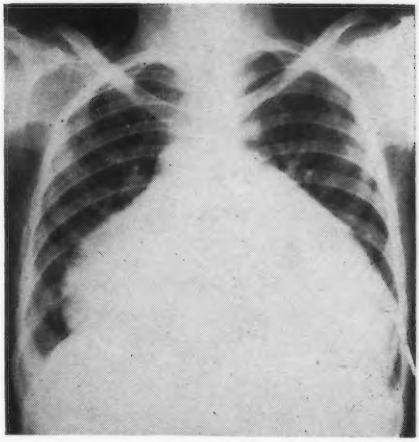

Figure 6

Pericardial effusion: Maximal distention of the pericardial sac. Notice the small centrally located vascular pedicle, the retracted cardiophrenic angle, and the relatively clear lung fields.

The Shapeless Heart

There exists a group of pathological hearts which, while moderately enlarged, do not show a particular chamber enlargement, do not displace the esophagus, and do not have points of opposite pulsation. No diameters can be drawn, as the walls are flaring, and under inspiration they give way to the pulmonary pressure. The ventricular walls are, indeed, sometimes caved in. A critical analysis of these cases is still lacking. In older persons they are frequently ascribed to myocardial degeneration or myocardial damage, but they are also found, perhaps less pronounced, in thyrotoxicosis, myxedema (with or without pericarditis), scarlet fever, typhoid fever, and after diphtheria.

Myocardial infarction due to coronary thrombosis (Figure 7) does not commonly change the heart size, but the size of the infarct and the adequacy of the collateral circulation permit considerable variation. It is not possible to ascribe this heart form entirely to myocarditis . . . and only cautiously is the diagnosis of myocardial damage made. The term myocardial exhaustion might more

Figure 7

The shapeless triangular heart: In this case due to a severe coronary occlusion, but frequently found in elderly patients without symptoms.

exactly cover the condition of the heart. Such a heart has thin walls, resulting in myogenic dilatation of the ventricle and marked changes in size during inspiration and expiration. Actual atrophy of the heart muscle may occur in older age, and hearts as small as fifty grams may be seen. In cases of amyloidosis of the heart, scleroderma, lupus erythematosus disseminata, and polyarteritis nodosa we have numerous variations of the heart shape, from the above described pyramidal shape to that of a globular shape. It is important to separate from the shapeless heart the one where the pericardium acts as a rather loose glove obscuring the heart shadow, which is one to two centimeters inside of the stretched pericardial shadow. A penetrating film will prevent this frequent mistake by contrasting the rounded inner heart shape with the straight-lined pericardial sac, which is frequently accentuated by fat deposits.

Importance of the Broncho-vascular Markings

No heart examination is complete without careful observation of the pulmonary artery and the vascular pattern of the lungs. Chronic lung disease and heart disease not only resemble each other frequently in x-ray observation, but they are concomitant. Disease and insufficiency in one system manifests itself in the other . . . "Man is indeed a heart-lung specimen" (Reid). Primary and secondary pulmonary hypertension may modify the vascular pattern and the width of the pulmonary artery, as well as the heart shape.

SUMMARY

Cardiothoracic measurements and ratios have been discussed.

Seriographic roentgenologic studies have been emphasized with regard to their superior value over the single film.

Five pathologic heart types, *viz.*, the mitral configuration, the aortic configuration, the combined lesion, the pericardial shape, and the shapeless heart have been discussed from a roentgenological point of view. The principle distinguishing features have been enumerated.

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SYMPOSIUM ON CARDIAC DISEASES:

V. PRIMARY SYSTEMIC AMYLOIDOSIS

Report of a Case Diagnosed Antemortem

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INTRODUCTION

Primary systemic amyloidosis is a rare entity and is to be distinguished from secondary amyloidosis, lichen amyloidosis, and from both local and tumor forming amyloid, as is seen in the urinary bladder and upper respiratory tract. The relationships of systemic amyloidosis seen in association with multiple myeloma are yet to be determined. The symptoms of this disorder depend upon the sites involved, but are not widely divergent, according to those reports reviewed. With only sixty-nine cases to be found since the first description in 1856 [1], we do not feel justified in making statements as to incidence rates of age, sex, color, or symptoms, but there does not seem to be any sex predilection and the symptoms usually become manifest in the fifth and sixth decades. There have been three previously reported cases in Negroes.

With only approximately seventy cases of primary systemic amyloidosis recorded in the literature, each additional report is valuable for the clarification of etiology and pathology. Since the symptoms are non-specific, being dependent upon the localization of the amyloid deposits, we shall devote our attention to a report of the pertinent clinical, laboratory, and autopsy findings, rather than to any extensive clinical discussion.

CASE REPORT

First Admission: On October 4, 1950, a fifty-one year old Negro housewife entered Mount Sinai Hospital because of shortness of breath on slight exertion, orthopnea, palpitations, and swelling of her abdomen and legs for the past three months. She could not recall any earlier symptoms. There was no history of rheumatic fever, hypertension, diphtheria, diabetes mellitus, scarlet fever, renal disease, malaria, or, in fact, of any previous illnesses other than unremarkable childhood diseases. She presented no evidences of syphilis or chronic suppuration. There was no known contact with tuberculosis. She had undergone twelve uneventful deliveries and had had one spontaneous abortion. During the present illness, her appetite was decreased but she had probably gained weight judging by the way her clothes fitted.

Physical examination: She was somewhat obese and was dyspneic at rest. Her temperature was normal. The skin, eyes, ears, nose, and throat were normal. There were no skin nodules and the tongue was normal. With the patient sitting in a semi-recumbent position, the jugular veins were distended bilaterally. Many non-tender, discrete, rubbery nodes about one centimeter in diameter were palpated in the neck. A large (3 x 2 x 1 cm.) submandibular node and several smaller discrete axillary and inguinal nodes were found. The heart borders were percussed fifteen centimeters to the left and three centimeters to the right of the midsternal line in the fifth interspace; there was no basal enlargement to percussion. The apex beat was poorly felt, and there were no thrills. The heart tones were poorly heard; the first mitral and second pulmonic sounds were accentuated; a systolic murmur was heard over the entire precordium. The pulse rate was ninety-two per minute, with occasional premature contractions. The blood pressure was 140/80; subsequent readings varied from 140/75 and 120/70.

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ACKNOWLEDGEMENT. We wish to express our appreciation to Dr. Harry J. Isaacs for permission to study and report this case.

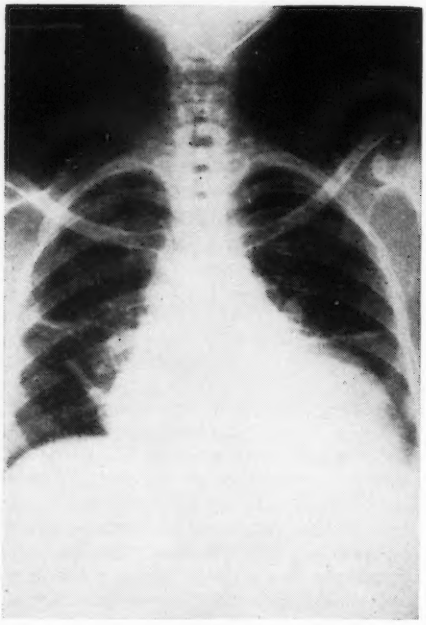

Figure 1

Chest roentgenogram showing an enlarged heart, hilar congestion, and hilar adenopathy.

The lungs were normal. The abdomen was globular. A small amount of free fluid was detected. A firm spleen was palpated four centimeters below the left costal margin and a firm liver was felt eight centimeters below the right costal margin, extending into the left upper quadrant. A firm nodule, about five centimeters in diameter was palpated at the edge of the liver near the umbilicus. She had slight sacral and three-plus pretibial pitting edema.

Pertinent Laboratory Findings

Hemogram: R.B.C.: 3,040,000; Hb..: 9.4 Gm.; W.B.C.: 7,600, segmented cells 60%, eosinophils 2%, lymphocytes 36%, monocytes 2%. Sickle cell preparation: negative.

Urinalysis: Specific gravity, 1.018; reaction, acid; albumin, 1+; sugar, faint trace (thereafter, negative); W.B.C., 6-8/HPF; R.B.C., 0; casts, 0.

Blood Chemistry: sugar, 109 mg. %; urea nitrogen, 8.5 mg.%; cholesterol, 114 mg.%; cholesterol esters, 67 mg.%; albumin, 4.3 Gm.%; globulin, 3.3 Gm.%; Cephalin flocculation, negative; thymol turbidity, 2.5 units; urea clearance, 87.2%; Congo red test, 46% retained in serum in one hour.

Serology: negative.

Frei test: negative.

P.S.P. excretion: 50% in one hour, 60% in two hours, 80% in three hours.

B.M.R.: plus 31.5; plus 28.0.

Electrocardiogram: Right axis shift; first degree A-V block.

Phonocardiogram: (Dr. A. A. Luisada) revealed "a rough systolic murmur having the maximum intensity over the pulmonic area; an auricular gallop is present at the apex."

Roentgenology: (Dr. J. Arendt)

10/10/50: "Examination of the chest reveals both hemi-diaphragms to be essentially normal in outline and contour. The bronchovascular markings are markedly increased. The pulmonary arteries appear slightly dilated. The heart is markedly enlarged in its transverse diameter. The cardiothoracic ratio is 0.66. There appears to be mostly left ventricular enlargement although there is most likely general enlargement of the heart in addition. The ascending aorta appears widened but the aortic knob does not appear prominent (Figure 1). In the right anterior oblique view after ingestion of barium, there is some posterior pressure on the esophagus by the left auricle. In the left anterior oblique view the enlarged left ventricle is again noted. Interlobar pleurisy is noted on the left side."

10/12/50: "Normal gall bladder. Liver is enlarged."

10/13/50: "There appears to be a mass behind the heart, just beneath the bifurcation of the trachea, which deviates the esophagus towards the left. This could be an enlarged left auricle with a thrombus within it."

10/18/50: (Laminography) "There appear to be two densities, a large one just below the carina, and a smaller one in the right hilar region. These could represent mediastinal tumors or glands or a thrombus in an enlarged left auricle."

11/11/50: "Numerous tiny translucencies are noted throughout the skull."

Hospital course: She received 1.4 mg. of digitoxin in three days and was given Mercuhydrin and a low salt diet. She responded excellently with almost complete disappearance of her complaints within five days. Her liver receded two centimeters but a minimal pretibial edema persisted.

On October 24 and November 4, nodes from the left axilla and left side of the neck were biopsied and showed amyloid deposits (Figure 2). A Congo red test was normal. In an effort to establish an unequivocal diagnosis, an exploratory laparotomy was done on November 27, 1950. Scant free fluid was found in the abdomen. The mass on the liver was a bile duct cyst. The liver was slate-gray and glistening. The spleen was firm and smooth, but not easily accessible through the incision. Rubbery, enlarged, discrete nodes were present retroperitoneally in the inguinal region. Biopsy of the liver revealed amyloid material in the periportal areas. Sections of the skin and muscle were normal. Post-operative convalescence was satisfactory and the patient was discharged on December 9, with the diagnosis of systemic amyloidosis, either primary or in association with multiple myeloma.

Comment: As the laboratory, cardiology, and x-ray reports returned, the diagnosis became increasingly perplexing. The electrocardiogram showed low voltage QRS complexes and a prolonged P-R interval (0.24-0.25 seconds), coupled with a right axis shift pattern. However, it was difficult to accept a rheumatic basis (mitral stenosis) considering the normal auscultatory lung findings, a phonocardiogram which showed no independent mitral murmurs, and a clinical history of multiple, uneventful full-term deliveries. X-rays of the chest did show evidence of pulmonary congestion, but no overt edema. The heart was referred to as enormously enlarged; the left ventricle and left auricle showed the most marked enlargement. Fluoroscopy substantiated this and revealed a well-pulsating left ventricle, thus diminishing the likelihood of pericardial effusion.

The hepatosplenomegaly, adenopathy, and normochromic anemia suggested the

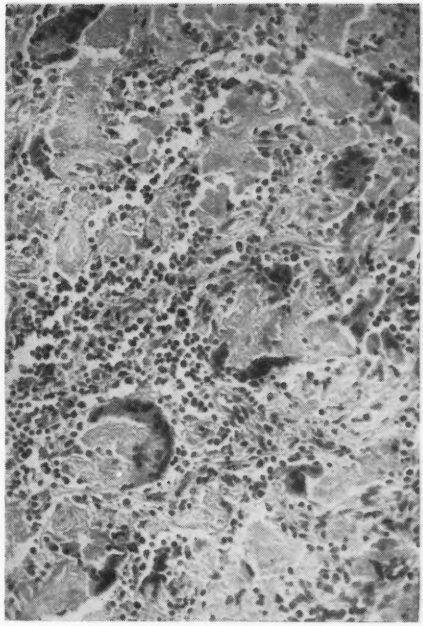

Figure 2

Microscopic section of biopsied cervical lymph node revealing replacement by amyloid material (x 150).

presence of a lymphoma or a carcinoma with metastases. At a Medical Staff Meeting discussing this case, primary systemic amyloidosis was also suggested.

The repeatedly elevated basal metabolic rates were ascribed to hypermetabolism secondary to low grade cardiac failure, or to a neoplastic process. Her original red blood cell count of three million slowly rose to over four million on the hospital diet. No source of blood loss was demonstrated. The white blood cell counts were not unusual, except for a six per cent eosinophilia on one occasion. The bleeding, coagulation, and clot retraction times, the platelets, and sickle cell preparations revealed no abnormalities.

Marrow from the sternum contained an increased number of normal plasma cells, but these were not arranged in sheets or nests and the other cellular elements were not remarkable. Because of this marrow picture, the slightly elevated serum globulin (3.3 Gm. per cent),

and the numerous small translucencies seen in the skull films, studies for Bence-Jones proteinuria were done. These were negative. However, the urine did show a persistent one to two plus proteinuria and, frequently, a slight pyuria. Roentgenograms of the long bones, pelvis, and vertebrae were normal. The blood urea nitrogen, P.S.P. excretion, and urea clearance tests were normal. Most of the liver function tests were normal, but the ability to esterify cholesterol was impaired; total cholesterol values were low (114-157 mg.%) and the ester fraction ranged from forty-three to fifty-five per cent. A Frei test was negative.

Having failed to establish any basis for the amyloid deposition, we classified the patient as being a case of systemic amyloidosis, either primary or of the type seen in association with multiple myeloma. When all the data were gathered, there was no reason to suspect hypertensive, luetic, arteriosclerotic, or congenital heart disease.

Second Admission: She was readmitted on March 17, 1951, because of increasing anorexia, weakness, palpitations, dyspnea, orthopnea, and ankle and leg edema. She had neglected her clinic visits and had taken no medication for about three months.

Physical examination: Her temperature was 102° F., pulse 88 per minute and regular, and respirations were 18 per minute at rest. The blood pressure was 110/78. She was pale and haggard. There was a pharyngitis and tonsillitis. The jugular veins were distended. A generalized adenopathy was noted and the upper mediastinum was widened to percussion. The lungs were clear and the heart was enlarged to the midaxillary line. Grade II apical systolic and grade I pulmonic systolic murmurs were heard; a gallop rhythm was present. The liver and spleen were enlarged as before and free abdominal fluid was present. There was definite sacral and leg edema. No significant changes in the laboratory and x-ray findings were noted. Two thousand cc. of straw-colored fluid were removed from the abdomen.

Hospital course: She responded poorly to a regime designed to relieve the cardiac decompensation. On March 30, she, as did other patients on the ward, developed a diarrhea which became profuse and bloody. Paregoric was given as the only additional medication. A few hours after the onset of the diarrhea, she developed an erythematous and urticarial skin reaction and complained of chest pain. Auscultation revealed wheezes in her chest. She received 25 mg. of Benadryl intramuscularly, and 3 minims of Adrenalin 1:1000 subcutaneously, with slight relief. The diarrhea became more severe and she died suddenly about two hours after the onset of the hypersensitivity reaction.

Autopsy Findings

The tongue was not enlarged. The larynx and nasopharynx were grossly normal. The peritoneal cavity contained about 300 cc. of clear fluid. The pleural cavities were dry, but the pericardial sac contained 350 cc. of dark red, watery fluid. The epicardium was smooth but showed petechial hemorrhages. The heart weighed 550 Gm. and was firm; the cut surface was a waxy, homogeneous pink. The iodine-sulfuric acid test gave a mahogany-brown color. The right and left ventricular walls were greatly thickened to ten and twenty-five mm., respectively; the valves were grossly normal; the coronary arteries and aorta were remarkably free of arteriosclerotic changes and presented no evidences of syphilis (Figure 3).

The lungs weighed 900 Gm. and were atelectatic in various areas, due to compression of large bronchi by enormously enlarged and matted nodes in the mediastinum and hilar areas. These nodes had a putty-like consistency and a waxy cut surface. Lymph nodes in other areas resembled those in the chest, and, in addition, many showed central yellowish foci of necrosis. The thyroid and adrenals were moderately enlarged and showed waxy cut surfaces. The kidneys together weighed 670 Gm.; they were congested and contained several cysts filled with clear fluid. Their sectioned surfaces were waxy, but not otherwise unusual; the pelves were normal. Bone taken from many areas contained a jelly-like marrow. No grossly visible

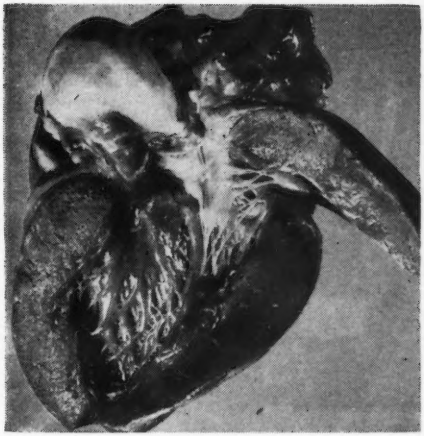

Figure 3

Grossly enlarged heart showing ventricular wall thickening due to amyloid infiltration. The aorta and coronary arteries were grossly normal.

areas of bony defect could be seen in the calvarium.

Histologic Anatomy

The microscopic tissue sections were stained with hematoxylin and eosin. Sections of the heart, lymph nodes, bone marrow, liver, spleen, and kidney were stained with Congo red and periodic acid leukofuchsin. Giemsa stain was used on bone marrow, lymph node, and spleen sections. Mosaic sheets of amyloid were seen throughout the myocardium; the myocardial fibers surrounded by this material were atrophic (Figure 4). The epicardium was similarly infiltrated. Small and medium sized myocardial and epicardial arteries presented nodular foci of amyloid in their walls. Other vessels in the epicardium were dilated and were in relation to the areas of interstitial hemorrhage. Broad-based, nodular projections of amyloid material were present on the endocardium.

The changes in the lymph nodes consisted of replacement of varying amounts of lymphoid tissue by pale pink-staining amyloid material arranged in irregular masses and sheets, surrounded by plasma cells, lymphocytes, eosinophiles, reticulo-endothelial cells, and multinucleated giant cells (foreign body type). There were interstitial hemorrhages and

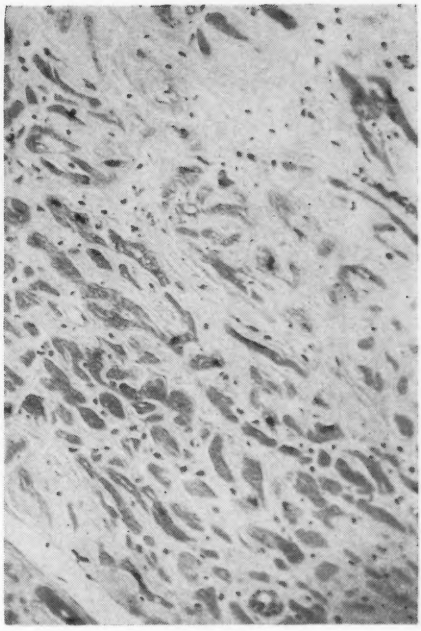

Figure 4

Microscopic section of the myocardium revealing marked amyloid deposition and myocardial fiber atrophy (x 150).

foci of necrosis with polymorphonuclear infiltrates.

In the bone marrow from various sites, including the suspicious areas in the skull, there were found large irregular masses of pale pink amorphous amyloid material, together with numerous multinucleated giant cells. The cellularity of all elements of the marrow itself was increased. No discrete myeloma lesions were observed anywhere (Figure 5).

The amyloid involvement in the liver was largely vascular and perivascular in the portal fields. The blood vessels were thickened; the fibrous tissue surrounding the vessels was infiltrated with lymphocytes, plasma cells, and a few eosinophiles. In the areas of more severe amyloid involvement and in areas of hemorrhagic necrosis within the lobules, there was an accompanying foreign body giant cell reaction. Scattered throughout were large cystic spaces, having a flattened laminated lining in which were pigment-laden Kupffer cells.

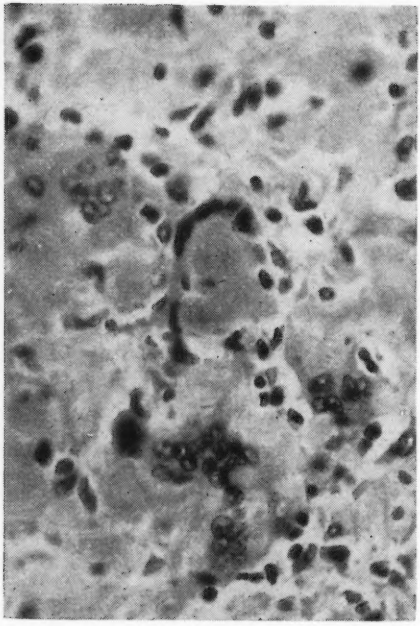

Figure 5
Microscopic section of the bone marrow showing marked replacement by amyloid material (x 550).

In the spleen, amyloid material had infiltrated into the thickened trabecles and into the central arterioles. Foreign body giant cells accompanied this change in various areas. One small focus of necrosis was observed.

Both adrenals were extensively replaced by amyloid in both the cortex and medulla, so that the usual cellular structure was not recognizable. In addition, there was a diffuse general infiltration by lmphocytes and plasma cells. There was also amyloid involvement of the blood vessel walls in the periadrenal fat tissues.

Sections of the kidneys revealed amyloid involvement of some glomerular tufts, and of the walls of small arteries and arterioles; the tubular changes were minimal. In the interstitial stroma there were diffuse and focal accumulations of plasma cells and eosinophiles and clusters of multinucleated giant cells. Throughout the parenchyma were found large cysts lined by a flattened or simple cuboidal epithelium, some of which had delicate papillary processes. A large focus of fibrous tissue containing atrophic tubules was noted in one area. The pelvic mucosa had an irregular epithelial lining and presented increased vascularity. The supporting tissue was richly infiltrated with mononuclear cells, mostly plasma cells.

In the lungs, pericardial sac, gall bladder, pancreas, and uterus, amyloid involvement was also observed, largely in the blood vessel walls. This involvement was frequently characterized by destruction of tissue and formation of granulomata containing plasma cells, lymphocytes, and foreign body giant cells. The lungs also presented a chronic bronchopneumonia and peribronchial amyloid involvement, but demonstrated no evidence of tuberculosis. In the thyroid and urinary bladder, the amyloid material was noted. In the dura mater, there were masses of amyloid material, within which foreign body giant cells could be seen.

COMMENT

The final anatomic diagnosis was primary systemic amyloidosis. This was based on the atypical location of the lesions in the heart, lymph nodes, bone marrow, thyroid, and fat tissue in addition to the so-called more typical sites in the adrenals, liver, and spleen; and on the failure to establish the presence of a primary pathologic state known to predispose to amyloid deposits. The minimal chronic inflammatory changes in the kidneys, plus the occasional pyuria, would suggest the possibility of a long-standing pyelonephritis. However, the argument is equally valid for regarding the renal changes as being secondary to the amyloidosis. Inasmuch as no definite lesions of multiple myeloma could be found anywhere, the plasma cell infiltrations were ascribed to the primary amyloidosis. This has commonly been noted under similar circumstances where the question of multiple myeloma in coexistence with systemic amyloidosis arises. Dr. I. Snapper[1] places diagnostic significance in the presence of Russell bodies in the plasma cells. These, he believes, indicate that the plasma cells

are part of a myelomatous process. Russell bodies were not noted in this case.

DISCUSSION

Clinically, this patient presented nothing that has not been noted before. She was in the usual age range of the fifth to sixth decades. The presenting syndrome of cardiac failure of unknown etiology has been common. However, in this case, the decompensation did not appreciably affect the left ventricle, but predominantly manifested itself as right heart failure. Why the right ventricle is predominantly affected in some cases is not known. The electrocardiographic patterns of right heart strain[7,8] and prolonged P-R interval[6,8,9] have been noted by others, but rarely occurred together[8], as in this case. Low amplitude of the QRS complex has been the rule; the low voltage is probably due to interference by the amyloid deposits with both the build-up and conduction of electrical forces. When present, pericardial effusion also contributes to the low voltage. The prolongation of the P-R interval is apparently due to deposits in the conduction system and has been noted quite frequently. Josselson *et al.*[11], noted a peculiarity in the V-leads of several electrocardiograms, *i.e.*, low voltage QRS complexes in the V_1 and V_6 leads with adequate voltage in the intermediate V-leads. These were also present in this case.

The presence of hepatosplenomegaly no longer can militate against the diagnosis of primary systemic amyloidosis; *i.e.*, amyloidosis is not necessarily limited to organs of mesodermal origin. Yet it may be that deposits in the liver, spleen, lymph nodes, and endocrine glands are derived solely from the capsular and blood vessel (mesodermal) elements.

In spite of the frequency of liver enlargement, disturbances of hepatic function are not common. Where reported, the cephalin flocculation, thymol turbidity, and the bromsulfalein retention tests are not distinctly abnormal. No generalizations can be made about the total protein, albumin and globulin values, or about the cholesterol and cholesterol esters, though the latter are usually in the normal range. Several cases have shown high cholesterol levels; three[3,4,5] of these were associated with milky serum. For no apparent reason, the levels in this case are the lowest reported. However, our patient manifested no other changes indicative of severe liver damage and was never icteric or cachectic. Frequently, the total protein levels have been lowered, but no constant pattern has been noted for variations of the albumin and globulin, whereas secondary amyloidosis, especially with renal lesions, is characterized by a low albumin and an elevated globulin.

SUMMARY

A case of primary systemic amyloidosis is reported. The diagnosis was suspected antemortem on the basis of biopsy material from lymph nodes and liver. Multiple myeloma was excluded by the autopsy findings.

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SYMPOSIUM ON CARDIAC DISEASES:

VI. CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. L. EDIDIN, Chairman DR. I. DAVIDSOHN, Secretary

Abstracted by DR. W. CLARKE

Clinical History

First Admission: This fifty-six year old white Jewish female entered Mount Sinai Hospital on March 24, 1951, complaining of a sudden swelling in her left breast. This swelling had been present for one week prior to admission, and there had been no pain or discharge from the nipple. A similar swelling of the same breast had been noted six years before; at that time she was informed that this swelling was a "gland." Following a hysterectomy at another hospital in July of 1950, she developed "pneumonia" and lost thirty pounds. The "gland" was not noticed again until this admission. Past history also revealed "rheumatic fever" at age nine.

Physical Examination: A hard, cherry-sized, freely movable non-tender mass was palpated just medial to the nipple of the left breast. A small, firm, non-tender node was also palpated in the left axilla. There was a mild malar flush noted, but there was no noticeable dyspnea, orthopnea, cyanosis, or edema. The lungs were clear. The pulse rate was ninety per minute and irregular. The heart was thought to be fibrillating. Mitral systolic and diastolic murmurs were heard, as well as a systolic murmur at the aortic area.

Hospital Course: The nodule in the left breast was excised on March 26, 1951. Pathologic examination revealed "cystic mastopathy, intraductal papillomas, and chronic, granulomatous inflammation."

The patient was discharged on March 28, 1951, in good condition.

Second Admission: The patient was readmitted to Mount Sinai Hospital on October 16, 1951, because of the appearance of a hard nodule in the right breast. This nodule had been present for about one month prior to admission, and there had been no pain, tenderness, or discharge from the nipple.

Physical Examination: A small, hard, non-tender, freely moveable mass was palpated in the lower inner quadrant of the right breast. There was no significant adenopathy noted. The rest of the physical examination was essentially unchanged from her first admission.

Hospital Course: On October 18, 1951, a mass was excised from the right breast. The pathologic examination of this nodule revealed "cystic mastopathy, intraductal papillomata, and chronic granulomatous inflammation."

The cardiac status was unchanged on this admission. The diagnosis at this time was: chronic rheumatic heart disease with (1) cardiac hypertrophy and dilatation; (2) auricular fibrillation; (3) aortic stenosis and regurgitation; (4) mitral stenosis and regurgitation.

The patient was well-compensated with 0.1 mg. of Digitoxin daily and a low salt diet. She was discharged in good condition on October 20, 1951.

Third Admission: The patient was again admitted to Mount Sinai Hospital on March 8, 1952, because of a sudden onset of pain in the right arm. The attending physician stated that the patient had developed embolic phenomena in the popliteal space with intermittent claudication approximately four months before this admission.

Physical Examination: On admission there was no pulse or blood pressure obtainable in the right upper extremity. The patient showed a mitral facies. No venous engorgement was noted. The lungs were clear. The apex beat was palpated in the sixth interspace at the anterior axillary line. A harsh systolic thrill was palpated in the second right interspace. A harsh systolic murmur

LABORATORY DATA

Blood counts:	RBC (mill.)	Hb (Gm.)	C.I.	WBC	Differential Count (in %) Stabs	Segs	Eos	Lymphs	Monos
3/24/51	4.30	13.0	0.96	10000	6	69	2	22	3
10/17/51	5.27	16.3		8550		66	2	25	7
3/10/52	4.15	13.6	1.00	18300	1	85	1	11	2
3/12/52				12200	3	66	2	19	10
3/19/52	4.24	13.9	0.99	9200		65	2	27	6
6/29/53	4.86	16.2	0.99	14950	3	69		19	9
7/16/53	5.14	17.6	1.03	15950	9	81		6	4

Blood chem:	T.P. (Gm.)	Alb. (Gm.)	Glob. (Gm.)	A/G ratio	Sugar (mg/100 cc.)	BUN	Chol.	Chol. Est.	Cl (mEq/L.)	Na	K
3/24/51					121	10.1					
10/17/51					103	12.8					
3/10/52	7.2	4.7	2.5	1.9	108	17.1			96.3	131	5.4
6/29/53					108	19.9					
7/6/53	6.9	4.3	2.6	1.7			180	56%	99.0		

Urinalyses: Negative on all admissions.

Serologic tests for syphilis: Negative on all admissions

Miscellaneous tests:

Blood culture: 3/18/52: No growth (final report)

ESR: 3/11/52 - Uncorrected - 32
Corrected - 32 Hematocrit - 42
6/29/53 - Corrected - 29 Hematocrit - 48

ECG: 3/13/52 - (1) Left heart strain
(2) Auricular fibrillation
(3) Coronary insufficiency

Prothrombin time: 6/29/53 - 15 sec.; **Clotting activity:** 57% of normal

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and a soft, machine-like diastolic murmur were heard at the aortic area. A crescendo systolic murmur and a mid-diastolic rumble were heard at the apex. The rate was ninety per minute and was irregular (auricular fibrillation). The liver was palpated three to four fingers below the right costal margin; it was smooth, slightly tender, and the edge was sharp. The blood pressure was 150/80 in the left arm and completely absent in the right arm.

Hospital Course: A complete work-up for bacterial endocarditis was negative. The patient improved with therapy and was discharged on March 22, 1952.

Fourth Admission: The patient's fourth admission to Mount Sinai Hospital was on June 27, 1953. Her husband stated that while talking to a neighbor, a short time prior to admission, she suddenly became dizzy and had to lie down for a short time. She was in a semi-comatose state and talked in a confused manner. Since her last hospitalization, she had been taking diuretics and digitalis daily.

Physical Examination: Physical examination revealed a well-developed, fairly well-nourished white female who was in no acute distress, but who was obviously confused as to time and place. The eyes, ears, nose, and throat were negative. The pupils reacted to light and accommodation. The lungs were clear to auscultation and palpation; breath sounds were harsh, but no rales were heard. A grade IV systolic murmur was heard over the entire precordium. A grade III diastolic murmur was heard over the aortic area, and a mid-diastolic rumble was heard at the apex. Liver dullness extended two centimeters below the right costal margin and the liver was felt two fingers below the costal edge. It was smooth, not markedly tender, and had a sharp

edge. The right radial pulse was absent. There was no evidence of paralysis. It was impossible to determine the degree of paresis present. Reflexes were hyperactive bilaterally, but no pathological reflexes were noted.

Hospital Course: On July 8, 1953, the patient stated that she felt well and wanted to go home. The cardiac findings were essentially unchanged and there were no cerebral symptoms. The patient was discharged in an improved condition on July 8, 1953.

Fifth (Final) Admission: The patient's fifth and final admission to this hospital was on July 15, 1953. She was in coma and no immediate history could be obtained. She was reported as having had a cerebral embolus ten days prior to this admission.

Physical Examination: The patient was comatose; stertorous breathing was noted. There was a flaccid left facial paralysis noted; the head and eyes turned towards the right side. No nuchal rigidity was noted. Moist rales were heard in both lung bases. An aortic systolic thrill was palpated. A harsh aortic systolic murmur was noted, as well as a mid-diastolic rumble at the apex. The liver was palpated three fingers below the right costal margin. It was smooth, non-tender, and had a sharp edge. There was a slight hyperactivity of the left patellar reflex; Babinski reflexes were noted bilaterally. There was also a positive Hoffman sign on the right.

Hospital Course: There was no change in the patient's condition following extensive therapy and she expired at 7:35 A.M. on July 18, 1953.

Clinical Discussion

*Dr. H. Kamin**: The electrocardiogram shows a rate of 60 per minute. The voltage of the QRS complex is rather tall. The T-waves are inverted in leads I and II. The S-T segments are depressed in lead II. We see some f-oscillations, which are characteristic of auricular fibrillation; there are no definite P-waves. The rhythm is irregular. In conclusion, we have a picture of left heart strain with auricular fibrillation.

*Dr. P. Silverio***: A chest film taken in March, 1951 (Figure 1), reveals slight congestion of the root shadows and moderate enlargement of the heart. There is a preponderance of the left ventricular segment, but there is no sign of infiltration in the lung. Another film, taken in October, 1951, reveals a moderate accentuation of the aorta and an enlarged left auricle. There is considerable preponderance of the left ventricle, which almost reaches to the left thoracic wall. There is some hilar congestion, but no infiltration of the lung parenchyma. This is a case of mitral-aortic disease.

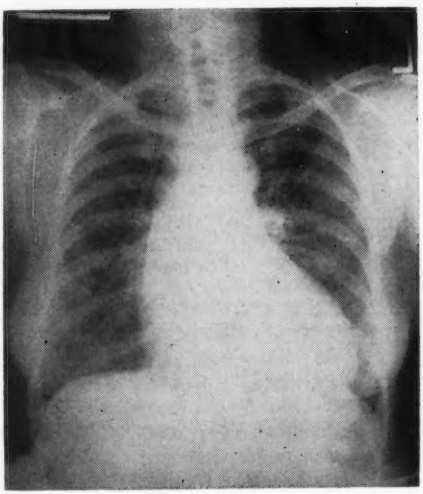

Figure 1

*Dr. L. Edidin****: I wish to correct the impression that the patient had rheumatic fever in childhood. I could never get that information from her in my office. She stated that she had never felt as well as other children did, and was always a little short of breath. At the age of nine she was told by a physician that she had a "bad heart," but she could not describe exactly what was wrong at that time. There were several

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other children in the family, and she apparently did not receive too much attention at home. She remained fairly well, however, until the age of thirty-seven, when she spent nine months in bed with a "weak heart." At that time, she was told by her physician that she probably would "never be able to get around very much." Thereafter she was fairly well until the age of fifty, when a hysterectomy was performed. The post-operative course was complicated by pneumonia; several weeks later a right-sided hemiplegia developed.

I first saw her in 1950, about four months after the hysterectomy. At that time, she was in heart failure with auricular fibrillation, congestion of the lungs and liver, and swelling of the legs. Treatment with diuretics and digitalis produced only moderate improvement. In addition, she presented weakness of the right upper extremity and dragging of the right leg. She was apprehensive, dizzy, and unsteady at times. Although these symptoms were not accurately described, I believe they were probably due to cerebral changes.

In 1951, at six month intervals, small nodules were removed from the left and right breasts, respectively.

In February, 1952, she complained of a sudden onset of pain and numbness in the left leg and foot. Oscillometric readings revealed normal oscillations of the right lower extremity; in the left there was increased pulsation above the knee and almost complete absence of oscillations below the knee, suggesting a block, probably embolic, in the left popliteal artery. A similar episode in March of the same year affected the right arm. The block in the right arm must have been proximal, because it was not possible to obtain either pulse or blood pressure.

Excessive perspiration and night sweats necessitated the consideration of bacterial endocarditis. However, the temperature was persistently normal, there were no petechiae, the spleen was never palpable, and blood cultures were negative.

The essential and predominant lesion in the heart seemed to be calcific aortic stenosis. There was a very rough, harsh, systolic thrill and murmur in the second right interspace near the sternum. In addition, a soft diastolic murmur was heard best parasternally in the third left interspace. A systolic murmur with a questionable diastolic rumble was audible at the apex. The most likely etiology of aortic stenosis is rheumatic fever. Congenital malformation of the aortic valve with superimposed infection and subsequent calcium deposits may cause calcific aortic stenosis after middle age. In this instance, though the disability began in childhood, it was associated with aortic regurgitation, auricular fibrillation, and questionable involvement of the mitral valve. Fluoroscopically there was narrowing of the retrocardiac space. These findings are more in accord with a rheumatic affliction, despite our inability to elicit an unequivocal history of rheumatic fever. While syphilis and arteriosclerosis may produce calcific aortic stenosis, neither diagnosis was seriously entertained in this case; the Wassermann was negative and the disease began at too early an age for arteriosclerosis. My final diagnoses are: (1) rheumatic heart disease with (a) calcific aortic stenosis and regurgitation, (b) possible mitral stenosis and regurgitation, (c) cardiac hypertrophy and dilatation, (d) cardiac failure with auricular fibrillation and chronic congestion of the lungs and liver; (2) multiple emboli to the extremities, lungs, and brain; the last cerebral embolus proving fatal.

Question: Did the patient receive hormone therapy?

Dr. L. Edidin: Yes, because of the night sweats and the possibility that they were menopausal in origin, she was given a trial of estrogenic treatment, but I think it aggravated her cardiac condition. She was in chronic cardiac failure for four years, and estrogens, as you know, may lead to retention of fluids. The nodules in the breasts also made me wary of hormone therapy.

*Dr. L. Feldman**: I agree that the patient had rheumatic heart disease, but I also think there was some infection

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present. Her white cell counts were 15,000 and 13,000 and the proportion of neutrophils was high. Such leukocytosis might possibly be accounted for by embolic phenomena, but she may also have had a recurrent endocarditis.

Dr. L. Edidin: As I previously stated, she had no clinical signs of bacterial endocarditis, except for excessive sweating. The high white cell count may be explained by chronic pulmonary congestion and emboli. Furthermore, leukocytosis, while suggesting infection, is not a sign of bacterial endocarditis. She also had a mild polycythemia. I would have expected an anemia and other findings of bacterial endocarditis after prolonged illness of four years duration. To keep everybody happy, I did give her penicillin for about a month; this produced no change in her cardiac status or in the leukocytosis.

*Dr. A. A. Luisada**: The case presented today looks so simple that I wonder if there is some catch. In subsequent examinations, different types of murmurs were heard. Was this because different men were listening to the heart or was the condition of the patient changing? For example, on the first examination, no mention was made of a diastolic aortic murmur. Different opinions of different listeners are common, so I would attribute these discrepancies more to different ears than to differences in the patient. I accept the statement of Dr. Edidin that there was no definite history of rheumatic fever. The patient was ill when she was a child, but the fact that she had a "bad heart" when she was very young—before the age of nine—may be interpreted as the result of either rheumatic or congenital heart disease. Both may be noticed between three and six years of age.

We should discuss those congenital heart diseases which give no cyanosis and permit survival to the age of fifty. That already restricts the possibilities. Could it have been coarctation of the aorta, aortic stenosis, or a septal defect? In septal defects, the murmurs are different from those described here. Coarctation is excluded, for we know that she had good pulsations in the legs. The most likely lesion, if congenital, would be aortic stenosis, or a bicuspid aortic valve, possibly with a superimposed rheumatic disease. We know that a bicuspid aortic valve is frequently the site of rheumatic or bacterial endocarditis.

The patient almost certainly had a combined aortic stenosis and insufficiency. It is true that the early diastolic murmur was heard to the left of the sternum, but that is not unusual, especially if the patient has a combined lesion of more than one valve. In general, calcific aortic stenosis gives only a systolic murmur and does not give a diastolic murmur, while a rheumatic lesion superimposed upon a bicuspid aortic valve might easily give both murmers. The electrocardiogram indicated a left axis shift, which would be in favor of a predominantly aortic lesion; but not exclusively, because patients with isolated aortic lesions very seldom fibrillate early. This patient started fibrillating early, which is more characteristic of a mitral lesion. So we return to the possible coexistence of mitral and aortic disease.

The various episodes of embolism are suggestive of mitral involvement, but may also be due in certain cases to "myxomata" of the left auricle following previous mural thrombosis. First is auricular thrombosis, then the formation of polyps which may detach themselves as emboli. The size of the left auricle in this patient was not evaluated too well by x-ray and I think that lateral and oblique views, especially with a barium swallow, would have shown the size of the auricle much better. It was, however, visible within the heart shadow and it did not seem to be very large. I noticed that the clotting time was less than normal. This would not favor embolism. I wish to remind you that similar patients have been given anticoagulant therapy in order to prevent repeated embolic phenomena.

There is one point which is somewhat curious. It is mentioned that during the fourth admission the liver was large and

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there was no pulmonary congestion. This is not unusual in some patients. For instance, in constrictive pericarditis or in tricuspid lesions, the blood is dammed before reaching the right ventricle and the pulmonary artery. In such cases, the pulmonary arterial pressure is lower than in the average mitral patient. Should we postulate lesions of more than two valves, *i.e.*, mitral, aortic, *and* tricuspid? I do not have enough data, but had I seen the patient or had there been a more detailed description, a definite decision could have been reached. Graphic tracings may also help in the diagnosis of such cases. In general, mitral patients with a tricuspid lesion have a persistently large liver with less disability. These patients who have no orthopnea frequently develop ascites and go on for years appearing to be more sick than they actually are. In this case, there was a severe lesion of the aortic valve which complicated the clinical picture.

A high sedimentation rate is mentioned several times, but always after embolism, which may have caused it. One might discuss whether the patient had a rheumatic recurrence or even a bacterial endocarditis. I see little proof or even suggestion of bacterial endocarditis. Rheumatic recurrence is quite possible but I seen no positive data except leukocytosis and deterioration of the patient. Many rheumatic patients sustain a low grade rheumatic activity which sometimes is not even confirmed by clinical or laboratory data and is only demonstrated by histological examination.

On the whole, I would say that the patient had rheumatic heart disease, having had rheumatic fever early in life; that she had a mitral lesion, and aortic stenosis with probable insufficiency, possibly superimposed upon a bicuspid aortic valve; that embolization started from either the mitral valve or from mural thrombi of the left auricle.

*Dr. M. M. Kirshen**: This seems to be a case of rheumatic heart disease with involvement of several valves; the dominant lesion being in the aorta. If the history as read is correct, the changing murmurs, with the progressive congestive failure, would indicate to me the possibility of a complicating infection. It could have been a recurrent activity of the rheumatic process or an engrafted bacterial endocarditis. The lack of fever, splenic enlargement, and other characteristic signs of the disease, does not always rule out such a diagnosis, even with failure to respond to penicillin. Additionally, the constant high monocyte count encourages me to suspect bacterial endocarditis.

Dr. L. Edidin: As stated previously, clinically this patient did not impress me as a case of bacterial endocarditis. A superimposed rheumatic infection would be more probable, although the length of time (four years) is somewhat against it.

Dr. L. Edidin's diagnoses:

Rheumatic heart disease with:
(1) calcific aortic stenosis and regurgitation;
(2) possible mitral stenosis and regurgitation;
(3) cardiac hypertrophy and dilatation.

Chronic passive congestion of the lungs and liver.

Multiple emboli to the extremities, lungs, and brain.

Dr. A. A. Luisada's diagnoses:

Rheumatic heart disease with:
(1) aortic stenosis and probable insufficiency (possibly superimposed on a bicuspid aortic valve);
(2) mitral stenosis and regurgitation.

Multiple peripheral emboli from either the mitral valve or from mural thrombi of the left auricle.

Anatomic diagnoses:

Rheumatic heart disease with:
(1) aortic stenosis and insufficiency;
(2) mitral stenosis and insufficiency;
(3) fatty degeneration of the myocardium, secondary to embolism from the damaged mitral valve;
(4) cardiac hypertrophy.

Chronic passive congestion of the lungs and liver, with early cirrhosis of the liver.

Infarction, recent and old, of the spleen and kidneys.

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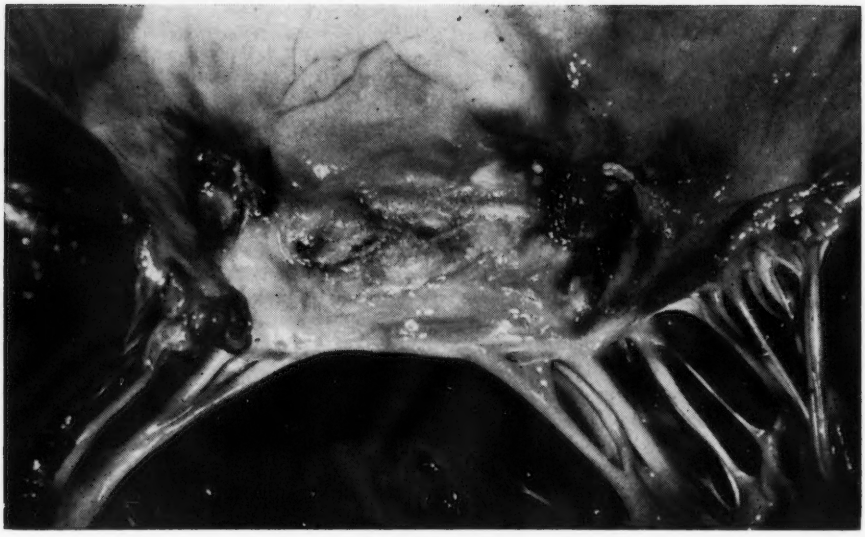

Figure 2

MITRAL VALVE: There is fusion of the leaflets which are markedly thickened and irregularly calcified. The chordae tendineae are thickened and shortened. The dark areas on the valve represent the sites of attachment of thrombi.

Pathologic Discussion

*Dr. Ira Gore**: The heart was very markedly enlarged. It weighed 650 grams, more than twice normal for a woman of this size. There were lesions of both the mitral and aortic valves.

A close-up of the mitral valve (Figure 2) reveals marked thickening. The commissures cannot be seen since stenosis results from the fusion of the individual valve cusps. Yellowish or brownish discolorations can be seen representing the sites of attachment of the thrombi which resulted in embolization. This was not a bacterial process. There are nodular deposits of calcium and marked thickening of the chordae tendineae, which are incorporated into the rigid and thickened valve leaflets.

The aortic valve (Figure 3) shows fusion of the individual cusps, with some visible remnants of a commissure. The individual cusps are thickened by fibrous tissue; they contain calcific nodules and are quite rigid. The valve was immobile; it could neither open nor close. I wish to draw your attention to two lesions, which, to the pathologist, indicate definite valvular insufficiency and stenosis. The first is a thickened plaque with a little valve pocket beneath the aortic valve. These form when the regurgitant current of the blood stream impinges against the ventricular wall, resulting in a reactive fibrosis of the endocardium. The second lesion is a sharply delineated plaque in the aortic wall. This forms as a reaction to a jet of blood spurting through the stenotic valve and impinging on the aortic wall. Thus, we have anatomic evidence of both stenosis and insufficiency. The valve itself had three cusps so there was no question of it being a congenital bicuspid valve.

When we examine the mitral valve microscopically, very marked thickening of the mitral leaflet is seen. It is twice the normal size. One can easily under-

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Figure 3

AORTIC VALVE: The fibrotic and partly calcified cusps are fused with almost complete obliteration of the commissures. Note the thickening of the endocardium below the valve, with formation of a small pocket, and the well-defined plaque on the aortic wall above the valve.

stand why it does not move as it should. The aortic valve is thickened to several times the diameter of the aortic wall, whereas normally the valve leaflet is quite a thin, filmy structure. There are nodular deposits of calcium in dense, fibrous tissue. Both the mitral and aortic lesions are of the kind seen resulting from previous rheumatic heart disease. Microscopically, there is no evidence of residual or active rheumatic infection, as indicated by Aschoff nodules. That is important, because we find something like twenty-five to forty per cent of patients with chronic rheumatic heart disease with no overt clinical evidence of activity, but with definite microscopic evidence of active rheumatic infection in the heart.

The heart muscle presented patchy areas of reddish discoloration and a few pale scars scattered through the left ventricular myocardium. This discoloration represents a weakening of the myocardium. There is an actual loss of substance due to muscle degeneration. This is the result of embolism from the diseased mitral valve. Damage of this sort further complicates the cardiac valvular insufficiency and nullifies the compensatory effect of the considerable myocardial hypertrophy.

In addition to the foci in which there is complete muscle loss, there are earlier degenerative changes in which the muscle fibers have lost their striations, are pale staining, and vacuolated. Fat stains demonstrate lipid material within these foci. This fat stain shows focal deposits of fat within the diseased myocardium. With progression, such damaged muscle becomes destroyed and is phagocytosed, leaving only the residual supporting stroma with a few inflammatory cells. Scarring is the natural evolution of such lesions.

The lungs were increased in weight and contained large quantities of blood and fluid, but no infarcts were seen. There were multiple infarcts in the spleen, which was small, weighing only ninety grams. It was quite firm and there were deeply indented areas of old infarction. In addition, other wedge-

shaped areas of yellowish color, representing more recent infarction were seen. Embolization apparently was going on for some period of time; the anatomic findings correlate well with the clinical picture.

The liver had extended two centimeters below the costal margin and was moderately enlarged, weighing 1600 grams; the normal liver weighs 1500 grams. It had a tense capsule and contained large quantities of blood. There was a mottled, nutmeg appearance on the cut surface. Microscopically one can see marked engorgement of the liver parenchyma; in the areas of long standing congestion there is atrophy of the liver cords with replacement by connective tissue. We therefore have an early cirrhosis developing as a consequence of chronic congestion.

The brain was not examined because of limitation of the autopsy consent.

Question: What was the condition of the coronary arteries?

Dr. I. Gore: The ostia were widely patent, but there was some sclerosis. Had she not had patent coronaries, she might not have had extensive myocardial damage, for the emboli would have been unable to gain entrance.

Dr. I. Gore (in reply to a question on the breast disease of the patient): The term cystic disease of the breast is a synonym for chronic cystic mastitis and it is generally recognized that this is not a truly inflammatory lesion. In fibrocystic disease, with enlargement of the cyst, there may be a loss of cyst epithelial lining with an inflammatory reaction to the contents of the dilated ducts and cysts. It is a form of chemical, rather than bacterial inflammation. That may account for the sudden symptoms in a patient with long standing breast disease.

Dr. I. Gore (in reply to a question about clotting activity): Low plasma prothrombin content may merely represent consumption of normal prothrombin in the process of clotting. Or it may mean less clotting activity—but it is no guarantee that clots or thrombi will not form, and it certainly does not prevent them. Here, there was a roughened surface and the circulatory condition with auricular fibrillation would predispose to the local formation of thrombi. Two possible explanations of the low prothrombin are: congestion of the liver with some degree of liver insufficiency and consumption of prothrombin during formation of the thrombi.

Dr. A. A. Luisada: This patient had several causes for coronary insufficiency. First, hypertrophy of the left ventricle. Beyond a certain limit, hypertrophy is not accompanied by a proportionate development of the capillaries, so that there is always some degree of relative ischemia. Second, the aortic stenosis lowers the mean pressure in the aorta and in the coronary arteries. Third, the aortic insufficiency lowers the diastolic pressure in the aorta and therefore decreases the possibility of a good flow through the coronary arteries. There were thus several possible explanations for the degeneration of the myocardium. Which of the causes determined localized softening I do not know. It is also possible that the patient had a coronary embolism; this is a rare occurrence, but in this patient, with so many emboli, it might well have taken place. The electrocardiogram that we saw did not show any evidence of a myocardial infarct, whether due to embolism or other causes. There was only evidence of the so-called "left heart strain" which is nothing else but anterolateral ischemia connected with the various processes which I have just mentioned.

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THE CHICAGO MEDICAL SCHOOL

QUARTERLY

710 South Wolcott Avenue
Chicago 2, Illinois

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